Chapter 8: Cardiovascular and Pulmonary Disease

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Key Points[a]

1. CVD is the commonest cause of morbidity and mortality in women [C].
2. The risk factors contributing to CVD are generally the same in women and men, with the possible exception of hormonal effects [C].
3. Evidence-based medicine has demonstrated that beta-blockers, aspirin, statins, and ACE inhibitors can reduce the risk of cardiovascular events in women. The main causes, prevention, and treatment of CVD in women are similar to those in men [A].
4. Although the use of HRT has been associated with a lower risk of CVD in epidemiological studies, this has not been borne out in clinical trials to date [C].
5. Until the long-term benefit of HRT is proven, attention should focus on identifying and treating the same risk factors in women as in men [A].

CVD is the commonest cause of morbidity and mortality in women.

1. Introduction

CVD afflicts more women than any other disease. It is by far the commonest cause of morbidity and mortality in women, and there is a steep increase in the incidence of CVD with age, especially after menopause. Ovarian hormones are thought to be protective of the cardiovascular system; 17β-estradiol and progesterone. Hormones that are effective for the short-term treatment of symptoms of perimenopause may not necessarily be the best choices for preventing CVD. HRT is not a single entity but encompasses a diverse number of agents, which may have differing effects on the cardiovascular system. It is therefore important, from a public health standpoint, to perform studies using different

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgment. (See also table 1–1.)

routes of administration and different doses and combination of hormones to arrive at firm conclusions about the role of HRT in the prevention of CHD in postmenopausal women. CHD prevention is conventionally divided into primary and secondary prevention. Primary prevention addresses interventions in the absence of clinically recognized disease, although atherosclerosis may be present. In secondary prevention, a cardiovascular event has already been documented. In this chapter we have made no distinction between primary and secondary prevention of CHD, since therapies that work for secondary prevention usually work for primary prevention and vice versa.

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Although HRT has been the focus of much attention in menopausal women, the approach to the prevention of CVD should be multifaceted. There is increasing information on the beneficial effects of lifestyle changes (e.g., nutrition and exercise), which can contribute greatly to the reduction in risk of CVD. One of the problems in CVD research in women is that some of the major pharmacologic studies have been conducted in men or have included only a small proportion of women. Nonetheless, a number of drug interventions, including beta-blockers, aspirin, statins, and ACE inhibitors, have been shown to decrease events associated with CHD in women as well as in men. Future studies have to include adequate numbers of women in order to make valid assessments of treatment effects in women.

This chapter identifies important areas of CVD that have been studied and reported in women and that provide a basis for future research in this area of women's health. Only with large, well-conducted clinical trials can important and accurate information be accrued on CVD in postmenopausal women.

2. Risk Factors for Coronary Heart Disease in Women

The term "risk factor" is used to describe characteristics found in healthy individuals that have been observed in epidemiological studies to be related to the subsequent occurrence of CHD. The risk factors for CHD are multifactorial, and many of these are similar in women and men.

- Age
- History of CHD, stroke, or peripheral vascular disease
- Family history of premature CHD
- Dyslipidemia
- Cigarette smoking
- Hypertension
- Diabetes mellitus
- Obesity (especially central)
- Lifestyle—diet, physical activity, psychosocial factors, alcohol
- Homocysteine and C-reactive protein (CRP)

Some risk factors are modifiable, such as smoking habit, alcohol intake, lifestyle, and biochemical and physiological characteristics. Other personal characteristics, such as age, gender, and family history of early onset of CHD, are nonmodifiable. Countries with high rates of heart disease in men also have higher rates in women; and conversely, low rates in men correspond to low rates in women (fig. 8–1). In developed countries, death rates for CHD in women aged 35–74 are decreasing (fig. 8–2); in contrast, rates are static or increasing in developing and eastern European countries. Women appear to be protected from CHD especially at younger ages, and it has been postulated that sex-specific hormones may be implicated.[2] Data from the Framingham Heart Study[3] reveal that the risk of CHD in an asymptomatic woman who has both elevated systolic blood pressure and smokes cigarettes is significantly less than the risk

FIGURE 8–1

Age-Adjusted Death Rates* for Coronary Heart Disease by Country and Sex, Aged 35–74, 1996†

* Age adjusted to European Standard.

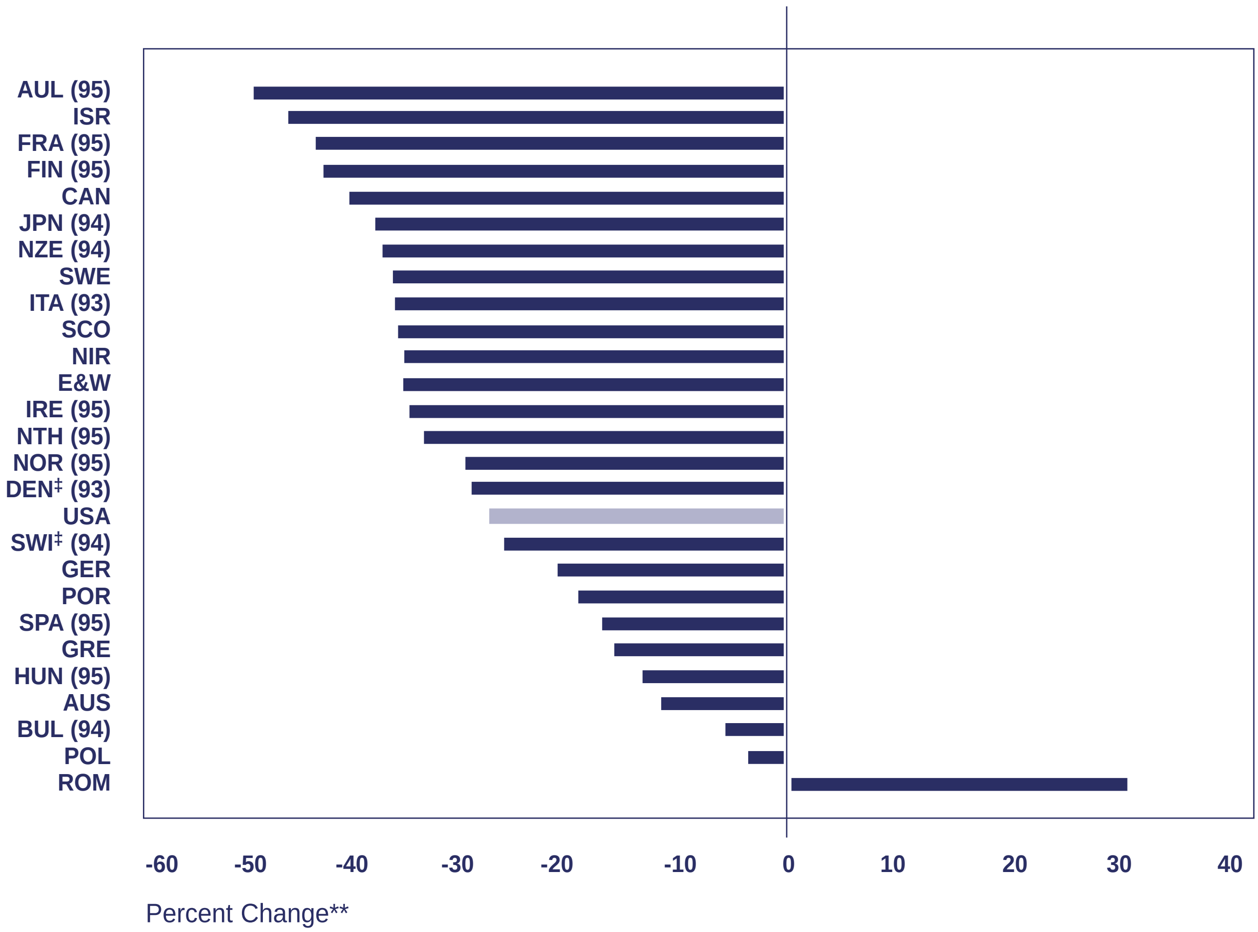
† Data for 1996 unless otherwise noted in parentheses.

‡ Eighth revisions of the ICD.

in a man of the same age. This applies to women and men at younger ages (age 50) but the differences between women and men no longer apply at older age (beyond the age of 80).[4] Established major modifiable risk factors for CHD in women, based on prospective studies, include raised total cholesterol (or LDL cholesterol), low high density lipoprotein (HDL) cholesterol, high blood pressure, cigarette smoking, diabetes, obesity, and physical inactivity. High triglycerides, raised Lp(a), and raised fibrinogen levels are also considered to be major risk factors by some authorities. The modifiable risk factors shown to be of cardiovascular benefit in randomized trials include

Figure 8–2

Change in Age-Adjusted Death Rates* for Coronary Heart Disease in Females by Country, Aged 35–74, 1986–1996†



* Age adjusted to European Standard.

** Based on a log linear regression of the actual rates.

† Data for 1996 unless otherwise noted in parentheses.

‡ Eighth revisions of the ICD.

reduction of blood pressure and blood cholesterol. Many studies have not included sufficient numbers of women to detect gender-specific differences. Factors such as homocysteine have clearly been identified as a risk factor in men,[5] and recent data suggest that higher homocysteine levels are observed among both male and female children with a positive family history of CHD:[6] in menopausal women increasing levels of homocysteine are associated with an increased risk of CVD.[7] More data are required before conclusions can be made about this and other postulated “new” risk factors, such as CRP levels.

2.1 Dyslipidemia

There is a strong graded positive association between plasma total cholesterol (or LDL cholesterol) and risk of CHD events in middle-aged (< 65 years) and older (> 65 years) women, but the strength of the association diminishes with age.[8] Although the general level of CHD risk is lower in women than in men, the association with total cholesterol remains powerful. Treatment of elevated total and LDL cholesterol in women has been shown to reduce CHD risk.[9] A low level of HDL cholesterol is a risk factor for CHD in both younger and older women.[10] Hypertriglyceridemia may be a more reliable risk factor for CHD in menopausal women than in men.[11,12] Lp(a) is associated with an increased risk of CHD[13,14] and is probably a determinant of CHD in both premenopausal and postmenopausal women.[15]

2.2 Cigarette Smoking

There is overwhelming evidence for an adverse effect of smoking on the risk of CHD and other vascular disease in women and men. The adverse effect of smoking cigarettes is dependent on both the daily amount smoked and the duration of cigarette smoking. However, the evidence derives from multiple observational studies rather than clinical trials.[16,17] The detrimental effects of cigarette smoking on CHD may be even more pronounced in women. In Europe, the impact of cigarette smoking on the risk of CHD is smaller in Mediterranean populations than in the northern European population.[18] Dietary factors probably explain this difference in the effects of cigarette smoking.

2.3 Hypertension

There is a strong association between high levels of blood pressure, both systolic and diastolic, and the risk of CHD in both women and men.[19] Isolated systolic hypertension is particularly important in older women as it affects up to a one-third of women older than 65 years and is associated with a significant increase in risk of CHD and stroke.[20] Treatment of older women in the Systolic Hypertension in the Elderly Program (SHEP) trial demonstrated a 25 percent reduction in CHD and a 36 percent reduction in stroke in both women and men combined,[21] as well as decreased late occurrence of heart failure.[22] In a meta-analysis of the trials, the greatest benefit of control of blood pressure of the trials is in subjects at high combined overall risk. Following a MI for example, elevated blood pressure is associated with an increased risk of reinfarction and death.[23]

2.4 Diabetes Mellitus

Diabetes mellitus is an important risk factor for CVD in women.[24] It negates the female sex-related differences in CHD prevalence, and diabetic women have as high a risk of MI as nondiabetic women with a previous MI.[25,26] Data from the Framingham Study show that for subjects aged 50–59 years, diabetes mellitus was a greater risk factor in women compared to men.[27] Even when corrections are made for other established risk factors, diabetes is associated with more than double the risk of CHD compared with women without diabetes.[26] Elderly women have a relatively high incidence of diabetes, contributing to a higher CVD risk. There are many reasons why a diabetic woman is at excess risk. She has dyslipidemia with lower HDL cholesterol, elevated triglyceride levels, and more atherogenic (oxidized) LDL.[28] Treatment of elevated LDL in diabetics reduces CHD risk.[29–31] Other factors include abnormalities of coagulation and fibrinolysis as well as abnormalities of platelet function. Endothelial cell dysfunction has also been shown in diabetics.[28]

There is overwhelming evidence for an adverse effect of smoking on the risk of CHD and other vascular disease in women and men.

2.5 Obesity

In the Third National Health and Nutrition Examination Survey (NHANES III), 55 percent of the adult female American population was classified as overweight or obese.[32] The cardiovascular health burden of obesity includes a strong predisposition to both type 2 diabetes and to hypertension. The prevalence of these conditions in the presence of obesity is increased by twelvefold and fivefold respectively, in women younger than 55 years.[32] Although there remains no causal evidence for the relationship between a sedentary lifestyle and obesity, the association between the two factors is strong.[33] In a female twin study, twins discordant for intensity of physical activity displayed significant differences in total and central body fat.[34] In that study, physical activity was the strongest predictor of total body fat, even after accounting for age, diet, smoking, and HRT. In an 18-month randomized behavioral study of sedentary obese women, there was a dose response effect of exercise duration on weight loss.[35] Women who were given access to home exercise equipment showed the greatest weight loss and maintained significantly greater exercise duration at the completion of the trial. HRT decreased central abdominal fat in a small prospective study of obese women with type 2 diabetes.[36]

Diabetes mellitus is an important risk factor for CVD in women.

Obesity in women is a complex metabolic disorder with strong genetic components. The peroxisome proliferator-activated receptors (PPARs) consist of three receptors α, β, and γ. PPAR-γ is expressed in adipose tissue. It has recently been shown that two polymorphisms in the PPAR-γ gene are associated with severe overweight among obese women.[37] The exact mechanisms by which the PPAR-γ variant affects adipose tissue mass are not known. Changes in the activity or structure of the PPAR gene in vivo may result in changes in expression of target genes in differentiating cells. Alterations in adipocyte differentiation may then lead to obesity.

2.6 Lifestyle

A number of lifestyle factors (other than cigarette smoking) have been implicated in CHD. These include diet, physical activity, psychosocial factors, and excessive alcohol intake. There appears to be a synergistic effect of lifestyle readjustments, such as the combination of diet, exercise and abstinence from smoking, in the primary prevention of CHD in women.[38]

2.6.1 Diet

Diet is an important determinant of CHD risk both in women and in men. Epidemiological studies show that diets low in saturated fat and high in fruits, vegetables, whole grains, and fiber are associated with a reduction in the risk of CHD. Consistent with early metabolic feeding studies, recent epidemiological studies suggest that replacing saturated and trans-unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats may be more effective in preventing CHD in women than in reducing total fat intake.[39] Clinical trials have shown reductions in CHD events or angiographic outcomes for a variety of dietary interventions: very low fat diets,[40] diets low in saturated fat and high in polyunsaturated fat,[41–42] a Mediterranean diet high in oleic acid and ω-3 fatty acids,[43] and diets rich in antioxidant fruits, vegetables, and legumes.[44] The effect of food supplements such as vitamins B6, B12, and folate, as well as flavonoids and soy isoflavones, require further investigation in clinical trials before firm conclusions can be made about their potential to favorably affect cardiovascular outcomes in healthy women and those with established CHD.

The use of alcohol has a U-shaped relationship with regard to the risk of CHD.

2.6.2 Physical Activity

Diet alone failed to lower LDL cholesterol levels in women with high-risk lipoprotein levels who did not engage in aerobic exercise. A combination of the NHLBI's National Cholesterol Education Program (NCEP) Step II Diet plus exercise beneficially reduced LDL cholesterol compared with the diet alone.[45] The Lifestyle Heart Trial showed that intensive lifestyle changes in both women and men with severe CHD resulted in regression of coronary atherosclerosis at both 1 and 5 years. The benefit was greater at 5 years.[40] In a cohort of women after coronary bypass surgery, depressed women (comprising 23 percent of the entire cohort) not only improved their mental health in response to a formal rehabilitation program but also lost more weight and increased their HDL levels to a greater degree than the nondepressed patients.[46] This study confirms that the benefits of an exercise program extend beyond weight reduction and fitness to include psychosocial and even risk factor modification. In a recent report from the Nurses' Health Study, brisk walking, as compared with vigorous walking, was associated with a similar and substantial reduction in the incidence of coronary events among women aged 40–60 years.[47]

2.6.3 Psychosocial Factors

Psychosocial factors, such as anger and hostility, are positive predictive factors for an increase in intimal medial thickness of the carotid arteries over a 10-year period; this may be predictive of early atheroma development.[48] In a Swedish study, lack of social support contributed to the severity of CAD in women, independent of standard risk factors.[49,50] Hostile attributes, fasting insulin level, and weight gain in mid-life, may contribute to the development of visceral adipose tissue in healthy menopausal women, which may then lead to the increase in risk of CHD. Socioeconomic status had an independent association with factor VII level, suggesting an increase in thrombotic tendency.[51]

2.6.4 Alcohol Intake

The use of alcohol has a U-shaped relationship with regard to the risk of CHD. Nondrinkers have a higher risk than moderate drinkers (10–30 g ethanol daily), but the risk increases with increasing alcohol consumption.[52] Importantly, alcohol intake in women may also be related to an increase in blood pressure and risk of breast cancer.[53]

2.7 Homocysteine and C-Reactive Protein

Increasing levels of homocysteine are associated with an increased risk of CVD in postmenopausal women.[7] Homocysteine has been shown to damage vascular endothelial cells, which may contribute to a consequent increase in the tendency to thrombosis. One study[54] demonstrated low plasma homocysteine levels in premenopausal women compared with high values in postmenopausal women, suggesting a close relationship between homocysteine metabolism and estrogen status. Several other studies demonstrated that HRT decreases homocysteine levels in postmenopausal women.[55–59] In some reports, this effect was found especially in women with initially elevated pre-treatment homocysteine values. Although recent data on vitamin B administration (as a potent homocysteine lowering drug) are promising, randomized clinical trials are needed to investigate whether decreasing plasma homocysteine levels by any means will result in a reduction of CVD risk in women.

With the recognition that atherosclerosis is an inflammatory process, several plasma markers of inflammation have been evaluated as potential tools for prediction of the risk of CHD. CRP appears to be a potent predictor of the risk of coronary events in postmenopausal women.[60] Adding CRP to lipid screening may provide an improved method of identifying women at risk for coronary events. A guide to risk reduction for women is given in the American Heart Association (AHA)/American College of Cardiology (ACC) Scientific Statement: "Consensus Panel Statement. Guide to Preventive Cardiology for Women" (table 8–1).[61]

Changes in vascular function directly attributable to menopause are difficult to identify.

2.8 Gender Differences in Atherosclerotic Plaque

Endothelial erosion and plaque rupture are regarded as sequelae of an inflammatory process involving activated macrophages and their response to oxidized LDL within the intima of the vessel wall.

TABLE 8–1

Guide to Risk Reduction for Women

Lifestyle Factors	Goal(s)	Screening	Recommendations
Cigarette Smoking	1. Complete cessation. 2. Avoid passive cigarette smoke.	1. Ask about current smoking status and exposure to others' cigarette smoke as part of routine evaluation. 2. Assess total exposure to cigarette smoke (pack-years) and prior attempts at quitting. 3. Evaluate readiness to stop smoking.	1. At each visit, strongly encourage patient and family to stop smoking. If complete cessation is not achievable, a reduction in intake is beneficial as a step toward cessation. 2. Reinforce nonsmoking status. 3. Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with behavioral therapy or a formal cessation program.
Physical Activity	1. Accumulate ≥ 30 min of moderate-intensity physical activity on most, or preferably all, days of the week. 2. Women who have had recent cardiovascular events or procedures should participate in cardiac rehabilitation, a physician-guided home exercise program, or a comprehensive secondary prevention program.	1. Ask about physical activity (household work as well as occupational and leisure-time physical activity) as part of routine evaluation. 2. In women with symptoms that suggest CVD or in previously sedentary women > 50 years old with ≥ 2 risk factors for CVD, consider a stress test* to establish the safety of exercise and to guide the exercise prescription.	1. Encourage a minimum of 30 min of moderate-intensity dynamic exercise (e.g., brisk walking) daily. This may be performed in intermittent or shorter bouts (≥ 10 min) of activity throughout the day. 2. Women who already meet minimum standard may be encouraged to become more physically active or to include more vigorous activities. 3. Incorporate physical activity in daily activities (e.g., using stairs). 4. Muscle strengthening and stretching exercises should be recommended as part of an overall activity program. 5. Recommend medically supervised programs for women who have had a recent MI or revascularization procedure.

TABLE 8–1 *(continued)*

Lifestyle Factors	Goal(s)	Screening	Recommendations
Nutrition	1. AHA Step I Diet in healthy women (≤ 30% fat, 8–10% saturated fat, and < 300 mg/d cholesterol). 2. AHA Step II Diet in women with CVD or if a further reduction in cholesterol is needed (≤ 30% fat, < 7% saturated fat, and < 200 mg/d cholesterol). 3. Limit sodium chloride (salt) intake to 6 mg/d. Women with high blood pressure may require further restriction. 4. Attain total dietary fiber intake of 25–30 mg/d from foods. 5. Consume ≥ 5 servings of fruits and vegetables per day.	1. Assess nutritional habits as part of a routine evaluation in all women. 2. Consider formal dietary assessment in women with hyperlipidemia, diabetes, obesity, and hypertension.	1. Encourage a well-balanced and diversified diet that is low in saturated fat and high in fiber. 2. Use skim milk instead of milk with a higher fat content. 3. Diets rich in antioxidant nutrients (e.g., vitamin C, E, and beta-carotene) and folate are preferred over nutritional supplements. Note: Daily supplements of 0.4 mg of folic acid are recommended for women of child-bearing age to help prevent neural tube defects. 4. Limit alcohol intake to ≤ 1 glass of alcohol per day (1 glass = 4 oz wine, 12 oz beer, or $1^1/_2$ oz 80-proof spirits). Pregnant women should abstain from drinking alcohol.
Weight Management	1. Achieve and maintain desirable weight. 2. Attain target BMI (weight in kilograms divided by height in meters squared) between 18.5 and 24.9 kg/m^2 (BMI of 25 kg/m^2 = 110% of desirable body weight). 3. Achieve desirable waist circumference of < 88 cm (< 35 inches) in women with a BMI of 25–34.9 kg/m^2.	1. Measure patient's weight and height, calculate BMI, and measure waist circumference as a part of a periodic evaluation. **Note:** BMI and waist circumference are used for diagnosis, and measurement of height and weight are used for followup.	1. Encourage gradual and sustained weight loss in persons whose weight exceeds the ideal weight for their height. 2. Formal nutritional counseling is encouraged for women with hypertension, hyperlipidemia, or elevated glucose levels associated with overweight. 3. The recommended weight gain during pregnancy is 25–35 lb if the patient's prepregnancy weight is normal. Adjust for multiple gestation and prepregnancy weight (e.g., overweight women should gain 15–25 lb, obese women, < 15 lb)

LV: Left Ventricular
SBP: Systolic Blood Pressure
TC: Total Cholesterol
TG: Triglycerides

*The choice of test modality should be based on the resting ECG, physical ability to exercise, and local expertise and technology.

†The ACC and the AHA recommend cholesterol screening guidelines as outlined by the NCEP (measure total and HDL cholesterol at least once every 5 years in all adults ≥ 20 years old. The consensus panel recognizes that some organizations use other guidelines, such as the U.S. Preventive Services Task Force, which recommends that cholesterol screening in women without risk factors begin at age 45 years.

Modified from Mosca L, Grundy SM, Judelson D, et al., 1999. [61]

TABLE 8–1 *(continued)*

<table>
<tr><th>Lifestyle Factors</th><th>Goal(s)</th><th>Screening</th><th>Recommendations</th></tr>
<tr>
<td>Psychosocial Factors</td>
<td>1. Adapt positively to stressful situations.
2. Improve quality of life.
3. Maintain or establish social connections.</td>
<td>1. Assess presence of stressful situations and response to stress as part of a routine evaluation.
2. Evaluate for depression, especially in women with recent cardiovascular events.
3. Assess social support system and evaluate for social isolation.</td>
<td>1. Encourage positive coping mechanisms for stress (e.g., substitute physical activity for overeating or excessive smoking in response to stress).
2. Encourage adequate rest and relief for women who are caretakers of others.
3. Consider treatment of depression and anxiety when appropriate.
4. Encourage participation in social activities or volunteer work for socially isolated women.</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>1. Achieve and maintain blood pressure < 140/90 mmHg and lower if tolerated (optimal < 120/80 mmHg).
2. In pregnant women with hypertension, the goal of treatment is to minimize short-term risk of elevated blood pressure in the mother while avoiding therapy that may compromise the well-being of the fetus.</td>
<td>1. Measure blood pressure as part of a routine evaluation.
2. Followup is based on initial measurement as follows:
<table>
<tr><th>SBP, mmHg</th><th>DBP, mmHg</th><th>Followup</th></tr>
<tr><td>< 130</td><td>< 85</td><td>Recheck in 2 yr</td></tr>
<tr><td>130–139</td><td>85–89</td><td>Recheck in 1 yr</td></tr>
<tr><td>140–159</td><td>90–99</td><td>Confirm in 2 mo</td></tr>
<tr><td>160–179</td><td>100–109</td><td>Evaluate in 1 mo</td></tr>
<tr><td>≥ 180</td><td>≥ 110</td><td>Evaluate in 1 wk</td></tr>
</table>
(Followup screening may be modified on the basis of prior history, symptoms, presence of other risk factors, and end organ damage.)
3. In pregnant women with hypertension, evaluate for preeclampsia.</td>
<td>1. Promote the lifestyle behaviors described above (weight control, physical activity, moderation in alcohol intake) and moderate sodium restriction.
2. If blood pressure remains ≥ 140/90 mmHg after 3 months of lifestyle modification or if initial level is > 160 mmHg systolic or 100 mmHg diastolic, then initiate and individualize pharmacotherapy based on the patient’s characteristics.
3. In pregnant women with hypertension, reduction of diastolic pressure to 90–100 mmHg is recommended.</td>
</tr>
</table>

TABLE 8–1 *(continued)*

Lifestyle Factors	Goal(s)	Screening	Recommendations
Lipids, lipoproteins	**Primary goal:** *Women without CVD* Lower risk (< 2 risk factors)LDL goal < 160 mg/dL (optimal < 130 mg/dL) Higher risk (≥ 2 risk factors)LDL goal < 130 mg/dL *Women with CVD*LDL ≤ 100 mg/dL **Secondary goals:** HDL > 35 mg/dL Triglycerides < 200 mg/dL Note: In women, the optimal level of triglycerides may be lower (≤ 150 mg/dL) and the HDL higher (≥ 45 mg/dL).	*Women without CVD** Measure nonfasting total and HDL cholesterol, and assess nonlipid risk factors. Followup is based on the following initial measurements: TC < 200, HDL > 45, followup in 5 years; TC < 200, HDL < 45, followup with fasting lipoprotein analysis. TC 200–239, HDL ≥ 45, and < 2 risk factors, followup in 1–2 years. TC 200–239, HDL < 45 or ≥ 2 risk factors, followup with fasting lipoprotein analysis. TC ≥ 240, followup with fasting lipoprotein analysis. (All cholesterol values in mg/dL) *Women with CVD* Fasting lipoprotein analysis (may take 4–6 wks to stabilize after cardiovascular event or bypass surgery).	1. Promote lifestyle approach in all women (diet, weight management, smoking avoidance, and exercise as described above). Rule out other secondary causes of dyslipidemia. 2. Suggested drug therapy for high LDL levels (defined as (a) ≥ 220 mg/dL in low-risk, premenopausal women, (b) ≥ 190 mg/dL in postmenopausal women with < 2 risk factors, and (c) ≥ 160 mg/dL with ≥ 2risk factors) is based on triglyceride level as follows: *TG < 200 mg/dL* Statin, Resin, Niacin Note: ERT is an option for postmenopausal women, but treatment should be individualized and considered with other health risks. *TG 200–400 mg/dL* Statin, Niacin *TG > 400 mg/dL* Consider monotherapy with statin, niacin, fibrate, or a combination of the above.
Diabetes	For patients with diabetes: 1. Maintain blood glucose: Preprandial = 80–120 mg/dL Bedtime = 100–140 mg/dL. 2. Maintain Hb $A1_c$ < 7%. 3. Maintain LDL < 130 mg/dL (< 100 mg/dL if established CVD). Note: Many authorities believe that LDL should be < 100 mg/dL in all patients with diabetes. 4. Maintain triglycerides < 150 mg/dL. 5. Control blood pressure.	1. Monitor glucose and hemoglobin $A1_c$ as part of a routine periodic evaluation in women with diabetes. 2. Screen for diabetes (fasting glucose > 125 mg/dL or > 200 mg/dL 2 h after 75 g glucose) as part of a periodic examination in women with risk factors for diabetes, such as obesity.	1. Encourage adoption of the American Diabetes Association Diet (< 30% fat, < 10% saturated fat, 6–8% polyunsaturated fat, cholesterol < 300 mg/d). 2. A low-calorie diet may be recommended for weight loss. 3. Encourage regular physical activity. 4. Pharmacotherapy with oral agents or insulin should be used when indicated.

TABLE 8–1 *(continued)*

Pharmacological Interventions	Goal(s)	Screening	Recommendations
HRT	1. Initiate or continue therapy in women for whom the potential benefits may exceed the potential risks of therapy. (Short-term therapy is indicated for treatment of menopausal symptoms.) 2. Minimize risk of adverse side effects through careful patient selection and appropriate choice of therapy.	1. Review the menstrual status of women > 40 years old. 2. If menopausal status is unclear, measure FSH level.	1. Counsel all women about the potential benefits and risks of HRT, beginning at age 40 or as requested. 2. Individualize decision based on prior history and risk factors for CVD as well as risks for thromboembolic disease, gallbladder disease, osteoporosis, breast cancer, and other health risks. 3. Combination therapy with a progestin is usually indicated in a woman with an intact uterus and prescribed estrogen. The choice of agent should be made on an individual basis.
OCs	1. Minimize the risk of adverse cardiovascular effects while preventing pregnancy. 2. Use the lowest effective dose of estrogen/progestin.	Determine contraindications and cardiovascular risk factor status of women who are considering the use of OCs.	1. Use of OCs is relatively contraindicated in women ≥ 35 years old who smoke. 2. Women with a family history of premature heart disease should have lipid analysis before taking OCs. 3. Women with significant risk factors for diabetes should have glucose testing before taking OCs. 4. If a woman develops hypertension while using OCs, she should be advised to stop taking them.

TABLE 8–1 *(continued)*

Pharmacological Interventions	Goal(s)	Screening	Recommendations
Antiplatelet agents/anticoagulants	Prevent clinical thrombotic and embolic events, DBP, in women with established CVD.	1. Determine if contraindications to therapy exist at the time of the initial cardiovascular event. 2. Evaluate ongoing compliance, risk, and side effects as part of a routine followup evaluation.	1. If there are no other contraindications, women with atherosclerotic CVD should use aspirin 80–325 mg/d. 2. Other antiplatelet agents, such as newer thiopyridine derivatives, may be used to prevent vascular events in women who cannot take aspirin.
β-blockers	Reduce the reinfarction rate, incidence of sudden death, and overall mortality in women after MI.	1. Determine if contraindications to therapy exist at the time of the initial cardiovascular event. 2. Evaluate ongoing compliance, risk, and side effects as part of a routine followup evaluation.	Start within hours of hospitalization in women with an evolving MI without contraindications. If not started acutely, treatment should begin within a few days of the event and should continue indefinitely.
ACE inhibitors	Reduce morbidity and mortality among MI survivors and patients with LV dysfunction.	1. Determine if contraindications to therapy exist at the time of the initial cardiovascular event. 2. Evaluate ongoing compliance, risk, and side effects as part of a routine followup evaluation.	1. Start early during hospitalization for MI unless hypotension or other contraindications exist. Continue indefinitely for all with LV dysfunction (ejection fraction ≤ 40%) or symptoms of congestive heart failure; otherwise, ACE inhibitors may be stopped at 6 wks. 2. Discontinue ACE inhibitors if a woman becomes pregnant.

Interesting differences in atherosclerotic plaque morphology between men and women have been reported. In a study of 113 cases of sudden death due to MI in men, 59 men had culprit thrombotic lesions, 69 percent of the lesions were due to atherosclerotic plaque rupture, and 31 percent were due to endothelial erosion.[62] This is in marked contrast to a study in women, which showed that 69 percent of the thrombi were associated with endothelial erosion.[63] These eroded plaques were characterized by smooth muscle cells and proteoglycans rather than lipid-laden macrophages. These data suggest that gender may influence plaque morphology, which may allow the development of gender-specific therapy in the future.

3. Menopause and Vascular Function

Changes in vascular function directly attributable to menopause are difficult to identify. Most studies have found little change in blood pressure associated with the menopause.[64–66] Healthy cohort studies suggest a change in endothelial function at approximately the appropriate age for the menopause to have an effect.[67,68] This is supported by a study which suggests that menopause is associated with an impairment in endothelial function, even in hypertensive women.[69] Whether these changes are due entirely to menopause or aging is not definite, as there have been no longitudinal studies to examine this question in detail. A recent review discusses menopause and vascular and ventricular function in depth.[70]

> ***Extensive concordant physiological evidence supporting an important role of HRT in the modulation of vascular function.***

3.1 Hormone Replacement Therapy and Cardiovascular Function

There is extensive concordant physiological evidence supporting an important role of HRT in the modulation of vascular function. This is particularly true in acute and chronic arterial endothelium-dependent effects, both in the periphery and in the coronary arteries. Apart from effects on responsiveness, arterial structural remodeling changes due to estrogen are suggested by animal models but have not been universally supported by large human cross-sectional studies. Clinical studies of aortic compliance have also led to inconsistent results. Studies of ventricular function are still limited and do not allow definitive conclusions. A consistent problem is the lack of prospective studies. Interpretation of studies which suggested a positive effect of HRT is limited by relatively small numbers and nonrandomized or unblinded designs.

3.2 Hormones and the Vessel Wall

A range of alternate mechanisms explaining the nonlipid-related cardiovascular benefit attributable to HRT have been proposed, particularly effects of hormones on the arterial wall. These actions are varied and include induction of endothelial prostacyclin,[71] improvement or restoration of endothelial function,[72,73] NO release,[74,75] attenuation of endothelin effect[76] and production,[77] calcium blockade,[78,79] direct effects on vascular depolarization[80] and smooth muscle relaxation,[81] and modulation of autonomic function.[82] Early reports of increases in renin or renin substrate may have been related to the higher estrogen doses used previously,[83] as recent work suggests that ERT is associated with decreased plasma renin substrate.[84]

A common endpoint of many estrogen actions, suggesting a beneficial effect, involves arterial vasodilatation. Systemic vasodilatation due to HRT has been associated with increased cardiac output and diminished systemic vascular resistance, both in experimental animals and in humans.[85,86] Coronary vascular reactivity has also been used as a surrogate marker for beneficial cardiovascular effect. Numerous studies have shown improvement in coronary diameter in response to estrogen,[87–89] particularly in the presence of atherosclerotic disease. Clinical studies have also shown decreases in exercise induced myocardial ischemia which may be due either to improved hemodynamics or direct coronary vasomotion.[90,91]

It has been suggested that the mechanism of estrogen action may vary according to the concentration of estrogen, with low concentrations relying on induction of NO release from the endothelium and higher concentrations being associated with smooth muscle relaxation and, therefore, endothelium-independent mechanisms.[92] A number of studies have confirmed improved endothelial function in postmenopausal women receiving HRT, both estrogen alone[72] and estrogen in combination with progesterone.[93]

The mechanisms by which estrogen alters vascular function have received extensive study, and the molecular mechanisms of its actions have recently been reviewed. (See also ch. 5.)[94] ERα is found on vascular smooth muscle cells[95] as well as endothelial cells.[96] Estrogen has also recently been shown to have nongenomic activity via ERα on the cell surface,[97] helping to explain acute vascular effects of estrogen found in numerous studies. The acute rapid ER-dependent but nongenomic actions result from activation of the MAPK cellular signaling pathway in a number of different cells.[98] The other known ER, ERβ, has been suggested to explain estrogenic action on both vascular smooth muscle and endothelial cell activity in ERα-deficient mice.[99]

Apart from estrogen, other sex hormones have significant vascular effects. Because estrogen is prescribed in combination with a progestin in women with an intact uterus, recent work has examined the modulating effect that this might have on cardiovascular function. Importantly, while the beneficial fibrinolytic[100] and lipid effects[101] of estrogen do not appear to be impaired with concurrent medroxyprogesterone use, experimental[102] and clinical studies[103] show how beneficial vascular effects of estrogen can be reversed by MPA. If further substantiated, these findings could be important in understanding results of some recently published studies, such as the HERS,[101] the first large trial conducted in postmenopausal women with CHD. (See sec. 4.2 below.) The effects of ERA[104] also showed no benefit either from estrogen or estrogen plus progestin in an angiographic study.

3.3 Selective Estrogen Receptor Modulators

SERMs have been developed to avoid the potential harmful effects of estrogen on a number of tissues, including the breast and uterus.

SERMs have been developed to avoid the potential harmful effects of estrogen on a number of tissues, including the breast and uterus. They appear to share the beneficial effects of estrogen on bone and lipids but are not associated with an increased risk of breast or uterine carcinoma, with the exception of tamoxifen, which increases endometrial cancer risk in women aged 50 years or older.[105] The possibility of a beneficial effect of SERMs on the cardiovascular system is intriguing. SERMs, such as raloxifene, have effects on both ERα and ERβ, which may be important in its vascular actions.[106] It is possible that SERMs may significantly contribute to the improvement of women's health in this century.[107] Evidence is emerging that the newer SERMs may have effects on cardiovascular and other systems which may contribute to improvement in vascular health and function. Research over the next 5 to 10 years may provide definitive data as to whether the newer SERMs will provide cardioprotection in postmenopausal women.

3.3.1 Effects of SERMs on the Vasculature

SERMs may have beneficial effects on the cardiovascular system in a way similar to estrogen. Randomized studies with cardiovascular endpoints are in progress.

3.3.2 Effects of SERMs on Serum Lipids and Myocardial Infarction

Studies investigating the effects of SERMs on serum lipids and lipoproteins have demonstrated similar effects in both patients with breast cancer and healthy women. The SERMs tamoxifen and raloxifene reduce total cholesterol, LDL cholesterol, and Lp(a).[108–110] These changes in lipid profile may be clinically favorable with regard to the incidence of CVD.[10,111] Data from randomized breast cancer clinical trials suggested that tamoxifen may be of benefit in protecting women from MI. Three adjuvant trials show a reduction of cardiac morbidity in patients with low risk of death from breast cancer when treated with tamoxifen,[112–114] although none of them had been designed for this purpose. The results of a cardiovascular endpoint study—RUTH (Raloxifene Use for The Heart)—will test whether raloxifene HCl (60 mg/day), compared with placebo, will reduce the combined endpoint of non-fatal MI, CHD death, and hospitalized unstable angina other than MI (primary outcome) in postmenopausal women at high risk of cardiac events.[115] A co-primary endpoint of invasive breast cancer incidence has been added to the primary endpoint.

3.3.3 SERMs and Vascular Reactivity

The PEPI trial confirmed that there was no effect of any hormone regimen on blood pressure in normotensive postmenopausal women.

There are few data on the effect of SERMs on the vasculature in humans. One report has shown a beneficial effect of droloxifene on brachial flow-mediated dilatation. Two conflicting reports have been published regarding the effect of raloxifene on atherosclerosis, one showing no effect in ovariectomized cynomolgus monkeys,[116] the other showing beneficial effects in sexually mature female rabbits.[117] The effects of raloxifene on coronary artery vasoreactivity in vitro showed significant dose-dependent relaxation of coronary arterial rings with endothelium by an endothelium- and NO mediated effect.[118]

3.4 Phytoestrogens

It has been suggested that phytoestrogens represent a "natural SERM." Genistein has approximately only 4 percent of estrogen's affinity for ERα, but more than 80 percent of estrogen's affinity for ERβ.[106] This marked difference may contribute to the conflicting findings on controlling menopausal symptoms.[119,120] The ERβ activity appears to be sufficient in in vitro studies to inhibit smooth muscle cell proliferation and migration compared with 17β-estradiol.[121] At least one study has shown that supplemental isoflavones may improve arterial stiffness in postmenopausal women.[122] A number of phytoestrogens, including genistein and daidzein, have calcium antagonistic properties in experimental coronary studies.[123]

Cross-sectional data show that as women age they gain body weight, their blood pressure rises, and their levels of serum LDL increase.

3.5 Hormone Replacement Therapy and Hypertension

Because hypertension is so prevalent in menopausal women and even low-dose contraceptive pills continue to be associated with excess hypertension,[124] there has been controversy over whether HRT may be beneficial or detrimental.[125] While most studies do not show an increase in blood pressure in response to HRT,[101,125,126] occasional patients have idiosyncratic increases in blood pressure in response to estrogen.[127,128] This may be related to excessive renin activation in these subjects.[127] Most case reports date from an era of higher estrogen dose, and it may be that current regimens would not incite such a response. A recent study using a current HRT regimen found, in general, a decrease in plasma renin substrate associated with treatment.[84] It has also been recognized that the type and dose of supplemental estrogen may be important in determining blood pressure response.[129] A well conducted crossover study of two doses of estrogen found a small, but significant, decrease in systolic and diastolic blood pressure largely due to a prominent fall in peripheral resistance.[130] Results from the PEPI trial confirmed that there was no effect of any hormone regimen on blood pressure in normotensive postmenopausal women.[126]

4. The Menopause and Coronary Risk Factors

Cross-sectional data show that as women age they gain body weight, their blood pressure rises, and their levels of serum LDL increase,[131] with little change in triglycerides and a slight reduction in HDL cholesterol.[64] Other blood factors such as serum fibrinogen and plasminogen activator inhibitor (PAI), which are powerful predictors of CHD in women and men are significantly increased in older women.[132] Abnormal glucose metabolism is more common in older women, with some reports showing approximately 30-percent reduction in insulin sensitivity.[133] Older postmenopausal women are more likely to have endothelial dysfunction,[69] which contributes to an impairment of vascular function and may synergize with the adversely altered lipid metabolism and decreased fibrinolytic tendency. These factors may collectively contribute to the increased incidence of CHD in older women.

It is not clear whether the adverse changes in risk factors are an age effect or are due to lowered estrogen levels as women go through the menopause. Cohort studies following women as they approach and pass through the menopause have yielded conflicting results, especially in regard to HDL cholesterol. Some concluded that the menopause is not associated with change in HDL cholesterol, while others concluded that the menopause is associated with a decline in HDL levels.[134,135] The most recent of these studies found an unexplained rise in HDL cholesterol prior to the FMP, followed by a decline thereafter; thus, there was no net effect.[136] The levels of HDL cholesterol 3 years before the menopause were identical to those 3 years after menopause. All other changes in the risk factors measured, including body weight, blood pressure, LDL cholesterol, and triglycerides, were related either to increasing age or to a simultaneous change in one of the other risk factors (in particular, increases in body weight).

4.1 The Effect of Hormone Replacement Therapy on Risk Factors

4.1.1 Lipids

Many studies have shown that that HRT lowers total cholesterol irrespective of the type or route of administration.[137,138] The LDL cholesterol-lowering activity of estrogen occurs by an up regulation of apolipoprotein-B–100 receptors. HDL cholesterol increases, particularly the HDL_2 subfraction, by an inhibition of hepatic lipase activity.[139] Although transdermal estrogen has a similar effect on LDL cholesterol, it has a less-marked effect on HDL cholesterol levels because of a lack of the first-pass liver effect.[140] Oral estrogen decreases LDL cholesterol by about 10–15 percent, increases HDL cholesterol by 10–15 percent, increases triglycerides by 20–25 percent, and decreases Lp(a) by about 20 percent.[126] The type and route of administration of estrogen are more important for its effects on plasma triglycerides than they are for its effects on cholesterol. While CEEs result in a 25-percent increase in triglycerides,[126] transdermal estrogen either has no effect or decreases triglycerides.[140]

Observational studies comparing current hormone users with non-users have shown consistent reductions in CHD risk of 35–50 percent.

Progestogens have differing effects on lipids and lipoproteins, dependent on the androgenicity of the particular agent. Testosterone-derived progestins reverse the HDL-increasing effect of estrogen[140] because of an increase in hepatic lipase activity. The less androgenic C–21 progestins do not impair the estrogen-induced increase in HDL cholesterol to any great degree. Androgenic progestins result in a lowering of triglycerides,[140] and the more androgenic steroids lower Lp(a) by approximately 20 percent.[141,142] This effect could prove beneficial as Lp(a) may be an independent risk factor for CHD in women.[15] Recent evidence from HERS suggests that Lp(a) is an independent risk factor for recurrent CHD events.[14] In the placebo arm of the study, women in the second, third, and fourth quartiles of Lp(a) levels had increased relative hazards compared with the lowest quartile. Treatment with HRT significantly reduced Lp(a) levels compared with placebo. In a randomized subgroup comparison, women with higher baseline Lp(a) levels had a less adverse-trend during the first year and more benefit thereafter.

4.1.2 Inflammatory Factors

Two studies of oral CEEs plus or minus MPA or progesterone have shown rapid increases in the concentration of the inflammatory factor CRP and a reduction in the concentration of soluble E-selectin.[143] In a cross-sectional study, CRP levels were increased in postmenopausal women taking HRT,[144] and in postmenopausal women exposed to short-term HRT of either oral estrogen or estrogen sequentially combined with a progestin.[145] In another prospective randomized controlled study of oral 17β-estradiol combined with 5 or 10 mg of dydrogesterone, there was a 15-percent decrease in plasma levels of endothelin-1, a 21-percent decrease in soluble thrombomodulin, and a 14-percent decrease in von Willebrand factor.[146] These changes were observed at 3 months and sustained after 15 months. It is possible that the increase in CRP is due to first pass effect on hepatic synthesis of the protein, while the decrease in markers of endothelial function and other inflammatory markers is due to direct vascular effects. It is unclear whether estrogen increases or decreases vascular inflammation or whether different forms, doses, and routes of administration have different effects on vessel physiology. One potential mechanism by which there may be an early adverse effect (such as that found in the HERS trial) followed by a later favorable effect is through effects on matrix metalloproteinases (MMP).[147] Preliminary reports indicate that MMP–9 is increased markedly by estrogen and may play a role in the destabilization of vulnerable plaques, thus precipitating a clinical event. However, over the long term, MMP–9 may help keep vessels compliant as it may play a role in removing excess connective tissue. Monocyte activation is associated with atheromatous plaque disruption and acute coronary syndromes (ACS). Increased serum concentration of neopterin, a pterydine derivative secreted by macrophages after stimulation by interferon-gamma, has been observed in patients with ACS as compared with control subjects and patients with stable angina pectoris.[148] Women with unstable angina have significantly higher neopterin concentrations than women with chronic stable angina. Neopterin concentrations may be a marker of risk in women with CHD.[149] HRT has also been shown to significantly reduce the levels of the cell adhesion molecules E-selectin, intracellular adhesion molecule 1 (ICAM–1) and vascular cell adhesion molecule–1 (VCAM–1) with similar magnitude of reduction from placebo values in women on CEE alone compared with women on combination HRT.[150]

Standard prevention therapies, including lipid lowering, are as effective in women as in men.

4.1.3 The Effect of Hormone Replacement Therapy Combined With Other Lipid-Lowering Agents

A number of studies have recently reported the effects of a combination of statin and HRT on serum lipid levels in menopausal women.[151–154] One study also assessed the vascular effects of this combination in hypercholesterolemic postmenopausal women.[155] The studies investigated the effect of differing doses of CEEs, either alone or combined with MPA, and compared the lipid-lowering effects to simvastatin or pravastatin.

Overall, these studies show that oral CEEs plus MPA in combination with a statin is complementary, in that the statins are better at lowering LDL cholesterol levels, the hormones are better at raising HDL cholesterol levels, and the effects on triglycerides cancel each other: thus the combination yields the most optimal lipid profile. The combination is only modestly additive, that is, hormones add little to the LDL-lowering effect of statins, and statins add only modestly to the HDL-raising effect of hormones. Hormones reduce Lp(a) levels, while statins do not. No studies have yet been published comparing other types and routes of administration of HRT combined with a statin.

In one study,[155] 28 women were randomized to continuous equine estrogen (0.625 mg daily), simvastatin 10 mg, and their combination daily for 6 weeks. As shown in the previous studies, all therapies lowered total and LDL cholesterol levels from baseline, with a greater effect on LDL cholesterol from simvastatin and from the combination of HRT and simvastatin. This study also assessed the vascular effects of this therapy; flow mediated dilatation of the brachial artery improved on CEE, simvastatin, and continuous equine estrogen combined with simvastatin, and this was similar among the therapies. Only therapies including CEE lowered levels of PAI–1 and the cell adhesion molecule E-selectin. Only therapies including estrogen improved markers of fibrinolysis and vascular inflammation. Thus, it may be that such a combination will be synergistic in vascular protection.

4.1.4 Coagulation Factors

The effects on coagulation factors are complicated, diverse, and contradictory. For example, lowering of fibrinogen and PAI–I could be counterbalanced by increases in factor VII and decreases in antithrombin III. In general, it appears that estrogen is procoagulant but, at the same time, profibrinolytic.[156] The net effect is likely to be procoagulant, as evidenced by the observational studies and the HERS clinical trial (see elsewhere). However, the net effect of estrogen on coagulation can depend on the form of estrogen used and on the dose, route, and duration of therapy. There may be critical differences between oral and transdermal delivery of estrogen. In contrast to oral administration, transdermal estrogen does not result in any measurable perturbation of coagulation factors.[156]

4.2 Hormone Use and Prevention of CHD Risk

Observational studies comparing current hormone users with non-users have shown consistent reductions in CHD risk of 35–50 percent. In the Nurses' Health Study, the risk reduction was seen at the most commonly used dose of CEEs (0.625 mg/day).[157] There appeared to be a similar risk reduction at the lower dose of 0.3 mg/day, but this was not statistically significant. At higher doses, there was no apparent benefit. The findings from these observational studies have been important in promoting the belief that HRT prevents CHD. However, the findings have to be viewed with caution because several sources of potential bias could result in an overestimation of potential benefits and an underestimation of risks.[158,159] These biases include that women who elect to take hormones are healthier, and those that remain on hormones for many years are by definition good compliers and are under medical surveillance. (See also ch. 4 for biases in sampling.) Thus, they would be taking other steps to improve their health, and early detection and treatment of risk factors would also reduce disease risk. Furthermore, women who stop therapy often do so because of the development of a health condition; thus those who remain on therapy are the healthy survivors. These biases

Women are approximately half as likely as men to receive known beneficial therapies, such as beta-blocking agents, aspirin, thrombolysis, acute cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), or bypass surgery.

may account for a substantial proportion (or all) of the apparent CHD risk reduction.

The information on the effects of hormones on lipids and markers of vascular function must be seen in the light of one very important fact: no clinical trial has yet shown a beneficial effect on any CVD. To the contrary, all the evidence to date suggests a harmful effect, at least in the first years of taking HRT. With the exception of the pooled data from a number of small short-term studies,[160] the clinical trials have all been in the area of secondary prevention. In men with CHD given higher doses of estrogen, the trials were stopped early for safety reasons after there was a higher rate of cardiovascular events in the treatment group than in the control group.[161] In HERS, women assigned to daily oral CEE plus MPA also experienced a higher rate of CHD events versus placebo in the first year, with no difference in the second year and with a trend toward decreased risk in the treatment group in the final 2 years. Over the entire 4.1-year study period, there was no difference between the groups. A reanalysis of the Nurses' Health Study observational data for women with prior heart disease disclosed a similar pattern of early risk followed by apparent benefit. The first placebo-controlled angiographic trial of estrogen or estrogen plus progestin also failed to show benefit in women with CHD.[104] Transdermal estrogen and progestin also failed to show benefit in a preliminary report of a randomized trial in women with CHD.[162] No clinical trial data on the role of HRT in primary prevention are available yet, but at least two large studies testing both estrogen and estrogen plus progestin are being conducted.[163] (WHI and the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)). The first of these, the large WHI trial of HRT in the United States, includes women predominantly without prior CVD and has arms testing daily CEE alone and CEEs with MPA versus placebo. All WHI participants were informed of an increased risk associated with active treatment for each of heart attacks, strokes, and blood clots in the legs and lungs during the first 2 years after enrollment.[164] The vast majority (> 90 percent) of participants did not have prior CVD, and the subgroup with prior disease did not account alone for the findings. Over time, the differences between the active treatment and placebo groups seemed to become smaller. The trial is continuing (estimated followup of 9 years) in order to assess long-term benefits and risk of HRT. There is a need for a clinical trial of transdermal estrogen, which may have less thrombotic potential than oral estrogen.

Gender remains a significant independent predictor of death after adjusting for other risk factors, such as older age, diabetes, and hypertension following PTCA.

4.3 Statin Use in Women and Reduction of CHD

Since evidence for a protective effect of estrogen is currently lacking, it is encouraging that the standard prevention therapies, including lipid lowering, are as effective in women as in men. This is not surprising since the RRs associated with blood lipids are the same in middle-aged women as in men.[8] One difference worth noting is that a combination of metabolic risk factors may occur more frequently in women and may account for a higher proportion of the CHD burden than in men.[165] For lipid lowering, the pooled data from the major statin trials show that women had a 29-percent (CI 13–42 percent) risk reduction, similar to the 31 percent (CI 26–35 percent) found in men.[9] From these data it has been calculated that 31 women and 27 men have to be treated to prevent 1 major coronary event. A gender bias does exist even in the statin trials that have been reported.[166] In the secondary prevention trials conducted, 31,683 patients were randomized with a combined mean age of 58.1 years, and only 23 percent of the trial population were women. The figures are even worse for primary prevention: in the four primary prevention trials published, only 10 percent of the study population, out of a total of 14,557 subjects, were women. It can be concluded that extrapolation of evidence from these trials to older people and women requires further evaluation.

4.4 Other Prevention Therapies in Women

Similar to the lipid-lowering trials, CHD prevention through treatment of hypertension is as effective in women as in men, and ACE inhibitors are as effective in preventing CHD in women as in men.[167–169] In the recently published Heart Outcomes Prevention Evaluation (HOPE) study, 2,480 women were enrolled as a part of larger study to determine the effect of the ACE inhibitor ramipril (10 mg once daily orally) versus placebo.[169] The study investigated the effect of this therapy over a 5-year period on the risk of the composite endpoint: MI, stroke, or death from cardiovascular causes. The study participants were patients at high risk for cardiovascular events with a mean age of 66 years an without left ventricular dysfunction or heart failure. Ramipril decreased the risk of the primary outcome significantly in women as well as men. There was also a significant decrease in secondary outcomes, such as revascularization and hospitalizations for heart failure. The novelty of this study is that ramipril significantly reduced the rates of the primary endpoint in a broad range of high-risk patients who were not known to have low ejection fraction or heart failure. In particular, this beneficial effect was shown in women with diabetes mellitus. The trialists that estimated the treatment of 1,000 patients with ramipril for 4 years prevented about 150 events in approximately 70 patients. Aspirin and beta-blockers are also effective for secondary prevention in women.[170,171] Thus, although efforts to prevent CHD in women are successful using the same approaches as in men, more data are still required.

5. Myocardial Infarction: Prognosis

Initial evaluation suggests that gender affects the course of acute MI in the general population. However, after adjustment for baseline differences, the gender disparities in the outcomes become more uncertain. In a study of 204 consecutive cases (99 men and 105 women) older than 75 years of age and admitted with the first acute MI, elderly women experienced a more complicated hospital course than men. The higher mortality risk (40 percent versus 23 percent) seemed to be related more to the impact of cardiovascular risk factors on left ventricular function than to gender itself.[172] The Framingham Heart Study confirmed a greater 1-year mortality in women compared with men (44 percent versus 27 percent).[173] Early hospital mortality is also greater in women than in men (16 percent versus 11 percent).[174,175] The larger placebo-controlled trials, such as the International Studies of Infarct Survival-1 and -4 (ISIS–1 and ISIS–4), both suggested an increased short and long-term mortality in women.[176,177] More recent data from the National Registry of Myocardial Infarction (NRMI) suggest that, after MI, younger women (but not older women) have higher rates of death during hospitalization than do men of the same age.[178] Data from the Swedish National Acute Myocardial Infarction Register confirms this observation.[179] Much of the excess mortality seen in young women in this study was associated with diabetes mellitus. Some other reasons for these observations is that women are approximately half as likely as men to receive known beneficial therapies, such as beta-blocking agents, aspirin, thrombolysis, acute cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), or bypass surgery; however, age probably still plays a major role in these differences.[171] Sex differences in the presentation and outcome of patients with ACS have been reported in the Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) cohort.[180] In this study, which enrolled 3,662 women, women had more complications than men during hospitalization, had a higher mortality rate at 30 days (6 percent versus 4 percent, $p < 0.001$), but had similar rates of reinfarction. It is of interest that among patients with unstable angina, female sex was associated with an independent protective effect. It was concluded from this study that some of the differences observed may reflect pathophysiologic and anatomical differences between men and women.

6. Percutaneous Transluminal Coronary Angioplasty

Most reports suggest that gender remains a significant independent predictor of death after adjusting for other risk factors, such as older age, diabetes, and hypertension, following percutaneous revascularization. Early studies suggested that women had a greater risk than men of procedural and postprocedural complications, including death and MI following PTCA.[181] Women have been found to suffer more acute vessel closure than men,[182] possibly related to their smaller vessel diameter. When acute closure does occur, women are more likely to die as a consequence of this.[183] An important contributor to higher procedure-related mortality in women is the greater age and coronary risk factor profile in women.[181,184] Nonetheless, analysis of the 1993–94 NHLBI registry has shown that despite their greater risk profile, both clinical success and mortality have improved twofold to threefold in women undergoing PTCA.[185] Many of the reported studies show that sex-related differences in mortality rate after intervention antedate the use of stents, platelet inhibitors, and other recent advances in coronary intervention.[186] In particular, intracoronary stent implantation (with optimal expansion) and ticlopidine have greatly reduced the incidence of acute vessel closure and significantly reduced the combined incidence of death, MI, and urgent revascularization after coronary intervention.[187] More recently, coronary artery stenting has become a very important catheter-based intervention for patients with CHD.[188] One-year outcomes of women with CHD undergoing coronary artery stenting are similar to those of men.[189] There is, however, a sex difference in the prognostic value of baseline characteristics, the strongest being diabetes in women. Other efforts at treatment synergy between intracoronary stenting and platelet IIb-IIIa inhibition are encouraging, showing an improvement in clinical outcomes of primary angioplasty in acute MI in both men and women.[190] The combination of abciximab and stenting was more favorable than balloon angioplasty, with improved angiographic and clinical results at 30 days. Analysis of the Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) data shows that diabetic women treated with a combination of coronary stenting and abciximab resulted in a significant reduction in 1-year rate of death, MI and target vessel revascularization compared with stent-placebo or balloon-abciximab therapy.[191] These recent advances in techniques may have changed the impact of acute vessel closure as a cause of death in women. The risk of acute complications was documented only in women undergoing PTCA for stable angina pectoris and not ACS. Long-term outcome is similar in the two sexes once the initial PTCA had been successfully performed.[192] Data from the Primary Angioplasty in Myocardial Infarction (PAMI) trial suggest that the two most powerful determinants of freedom from death, reinfarction, and recurrent ischemia are young age and treatment by primary angioplasty.[193] This initial benefit of primary angioplasty is maintained over a 2-year followup.[194] Recent reports from this database would suggest that coronary stenting provides even greater benefit than balloon angioplasty in the acute MI setting.[195] Recent data provide evidence that in primary PTCA for acute MI, gender is not an independent predictor of 30-day and 7-month survival after control for baseline characteristics. However, mortality was much higher in women both at 30-day followup (10 percent versus 0.9 percent) and during a mean 7-month followup (15 percent versus 4.4 percent). Women

Despite a similar prevalence of heart failure in women compared with men, women have largely been excluded from clinical trials of heart failure.

also experienced more unfavorable cardiovascular events, such as recurrent unstable angina or acute MI, and target vessel revascularization than men.[196]

6.1 Hormone Replacement Therapy and PTCA

Some studies have reported a benefit of outcome of PTCA in postmenopausal women if they were already receiving HRT. In a study of 428 patients, postmenopausal women divided into two groups based on ERT at the time of the procedure, there appeared to be protection against clinical coronary events in those women taking HRT.[197] This benefit appeared to be independent of age, smoking, presence of diabetes mellitus, or the number of diseased coronary vessels. HRT did not, however, reduce the repeat revascularization procedures, suggesting no effect on restenosis.[197] One study suggested a decrease in restenosis in women using estrogen, which was particularly apparent in women undergoing atherectomy, an effect which could relate to this procedure.[198] An improved long-term outcome after PTCA in women on HRT was also reported by another group.[199] In this observational study women taking ERT prior to intracoronary stenting had a significantly reduced target lesion revascularization requirement after a three year follow up when compared to women not taking estrogen prior to the procedure. This adds support to the notion that women should continue ERT after intervention if they are taking it prior to the intervention. Overall, HRT appears to be beneficial in women who continue to take it after percutaneous revascularization procedures; however, these conclusions are based on observation and could be confounded by a number of variables.

7. Coronary Artery Bypass Graft Surgery

Women undergoing coronary artery bypass graft (CABG) surgery are, on the whole, older than males and more frequently have associated risk factors, such as diabetes and hypertension. They are also more likely to present with unstable angina consequently, resulting in urgent/emergency surgery. It is not surprising, therefore, that women show higher rates of mortality[200] and recurrent angina.[201] Adverse operative and long-term mortality was shown in a large study, the National Cardiac Surgery Database of the Society of Thoracic Surgeons (STS), which compared outcomes in more than 97,000 women with those in 250,000 men.[202] In the Bypass Angioplasty Revascularization Investigation (BARI) study, a stable population of 489 women with symptomatic multivessel CHD was randomized to CABG surgery or PTCA.[203] Although the age-adjusted mortality rate suggested that women and men undergoing these procedures should have a similar 5-year mortality, when these were adjusted for multiple risk factors, female sex was an independent predictor of improved 5-year survival after surgery. This was a study of stable patients and patients, requiring urgent CABG surgery were excluded, which may have contributed to the more favorable result.[203]

Women undergoing CABG surgery show higher rates of mortality and recurrent angina.

Effective secondary prevention programs do not appear to be effectively instituted in women following CABG surgery. After CABG surgery, women continued to have high cholesterol levels, putting them at higher risk for future events.[204] This is particularly important since in women aggressive cholesterol lowering in women delays saphenous vein graft atherosclerosis and should be recommended to all women undergoing this procedure.[205] This obviously may contribute to poorer postsurgical survival.

7.1 Quality of Life After CABG Surgery

Women generally report a worse quality of life after CABG surgery than men. In a study of 212 women who underwent CABG surgery in 1988–1991, quality of life was assessed.[206] Women were older than men with more concomitant diseases preoperatively. Quality of life was improved on all postoperative occasions for both sexes. Improvement in the physical activity score was greater in males, although this was not significant. It appears that the quality of life is significantly improved after CABG surgery in both sexes, and there appears to be a complex association between improvement in various aspects of quality of life and gender.[205] Women's patterns of exercise following cardiac rehabilitation are well below the recommended guidelines for exercise after cardiac events.[207] In 40 women who had MI or CABG surgery, exercise frequency and duration intensity were measured. In a 3-month study, only 50 percent of the women were still exercising regularly, suggesting that there is considerable room for improvement in establishing exercise regimens after MI or CABG surgery. Women are less likely to be referred to rehabilitation.

8. Heart Failure

Despite similar stroke rates, women are more likely than men to die of stroke, and this is possibly related to the age at which stroke presents. About 16 percent of women die of stroke compared with only 8 percent of men.

Despite a similar prevalence of heart failure in women compared with men,[208] women have largely been excluded from clinical trials of heart failure. As discussed earlier, women tend to be older at presentation with cardiac disease and may fall outside recruitment guidelines. Secondly, women are more likely than men to have diastolic heart failure and may be excluded when systolic ejection fraction is an entry criterion.

Two large studies have reported improved survival in women with heart failure.[209,210] Of the randomized trials with beta-blockers in heart failure, the U.S. Carvedilol Heart Failure Study group found a statistically significant reduction in the number of deaths in both women and men with heart failure.[211] Other large beta-blocker trials have not been able to discern a sex-specific mortality difference.[212–214] In the trials of ACE inhibitors in heart failure, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS-I) did not show a reduction in mortality in women.[215,216] However, most trials contain such small numbers of women that they are unable to discern a specific mortality benefit for women. A meta-analysis of ACE inhibitor trials has shown a similar survival benefit for both women and men.[217] In the Acute Infarction Ramipril Efficacy (AIRE) study of ramipril in patients with post-MI left ventricular dysfunction, there was a significant mortality benefit in both sexes.[218] Three other studies of ACE inhibitors in patients with left ventricular dysfunction after MI did not show a significant mortality benefit for women. Again, this may be due to the relatively small numbers of women included in these trials.[219–221]

9. Stroke

Despite similar stroke rates,[222] women are more likely than men to die of stroke, and this is possibly related to the age at which stroke presents. About 16 percent of women die of stroke compared with only 8 percent of men.[222] Age is an important predictor of survival in stroke victims, and as the incidence of stroke is increased in older women, this contributes to the adverse mortality. The main risk factors for stroke are fairly consistent and nongender dependent. Hypertension probably is the most important, with diabetes mellitus, cigarette smoking, CHD, atrial fibrillation, and transient ischemic attacks comprising the major other risk factors.[223] Hypertension is a major risk factor for stroke, with about a 45-percent increase in stroke risk for every 8 mmHg increase in diastolic blood pressure.[19] Unlike many cardiovascular trials, hypertension treatment has been definitively shown to substantially reduce the morbidity and mortality in women following stroke. Studies such as the Swedish Trial in Old Patients (STOP) and

SHEP have shown that drug treatment reduces the incidence of stroke in hypertensive women.[167,168] Current smoking is associated with an increased risk of stroke, and in the Nurses' Health Study this increased the RR for ischemic stroke by 2.5.[224,225] Diabetes mellitus doubles the risk of ischemic stroke, and also increases the mortality associated with stroke. Cardiovascular conditions such as abnormal left ventricular (LV) wall motion, increased LV mass, carotid artery stenoses, and atrial fibrillation are significantly associated with an increased risk of stroke. Although elevated blood cholesterol is not a powerful risk factor for stroke, lowering of LDL cholesterol with statins reduces stroke risk. A meta-analysis of the statin trials done for CHD risk reduction showed a statistically significant 29-percent risk reduction for stroke, accompanying the 33-percent risk reduction for CHD.[222,226] Transient ischemic episodes are also related to an increased risk of subsequent stroke.[227] Use of HRT has been associated with a lower risk of fatal stroke, but no change in overall incidence of stroke, compared to nonusers. In the Nurses' Health Study, current hormone use was associated with an increased risk of ischemic, but not hemorrhagic, stroke. For all strokes, there was a dose-response effect, with higher doses of estrogen associated with a higher risk.[228]

In terms of active treatment of stroke, there are no clear recommendations. Early administration of aspirin seems to reduce the stroke-related death and recurrence, as shown in the Chinese Acute Stroke Trial (CAST).[229,230] Where transient ischemic episodes and stroke are associated with atrial fibrillation, warfarin may reduce the risk of stroke.[231] Carotid endarterectomy and aspirin therapy may be helpful in symptomatic severe carotid stenoses.[232] The only clinical trial to assess the effect of continuous CEEs combined with MPA is the HERS trial.[233] Over a followup of 4.1 years, 149 women had 1 or more strokes out of a total of 2,763 women. HRT was not significantly associated with risk of nonfatal or fatal stroke or transient ischemic attack. It was therefore concluded that HRT had no significant effect on the risk of stroke in this higher risk group of menopausal women with CVD.

10. Peripheral Vascular Disease

Peripheral vascular disease occurs relatively commonly in women, and like all CVD, there is an accelerated incidence with age in women.[234] Smoking is the most prevalent risk factor for peripheral vascular disease in women, as it is in men.[235] Insulin resistance, increased BMI, elevated fibrinogen, and elevated blood pressure are also risk factors.[235–237] Cessation of smoking and treatment of the underlying metabolic problem, if possible, may lead to improvement. Peripheral vascular disease carries an increased risk for CHD, which is nongender-dependent.[237] If surgery is indicated for severe peripheral vascular disease, smoking cessation is essential, and antiplatelet therapy may also be helpful.[238,239] The effect of HRT on peripheral vascular disease is not known.

There is an increase in risk of venous thromboembolic events in women taking estrogen compared with those that do not.

11. Venous Thromboembolism

Recent epidemiological studies and limited clinical trial data have shown consistently that there is an increase in risk of venous thromboembolic events in women taking estrogen compared with those that do not. The studies to date indicate that there may be a fourfold increase in RR initially, with a persistent twofold increase in risk thereafter.[240–243] The increased risk for venous thromboembolism was similar in women using an estrogen plus a progestin.[240,243] In unselected women, observational studies report an annual incidence of 6–18 events per 10,000 in subjects of all ages; thus a twofold increase in risk due to HRT might result in an excess risk of 6–18 per 10,000 per year, and a fourfold increase might result in 18–54 excess cases per 10,000 per year. The recent large randomized HERS study reported a statistically significant increase in risk of venous thromboembolic events among women randomized to hormone compared to placebo.[101] In a more detailed evaluation of the HERS population,[244] HRT was associated with a relative hazard of 2.7 and an excess risk of venous thrombosis of 39 events per 10,000 women per year. This higher risk was associated with older age, lower limb fractures, and cancer. An interesting observation was that the relative hazard for pulmonary embolism appeared to decline with time, but the relative hazard for deep venous thrombosis did not. This may have been a chance finding. The relative hazard for venous thrombosis seemed to remain elevated for 30 days after the discontinuation of HRT. The mechanisms for the increase in venous thromboembolism may involve alterations in coagulation factors; to date, no clear mechanism has been identified. Possible interactions with deficiencies of antithrombin-III, protein C and S, the prothrombin 20210G→A mutation, and factor V Leiden may result in the increased risk for venous thromboembolism. The interaction of activated protein C resistance with estrogen or estrogen plus progestin therapy has been confirmed in at least one study.[245] Women with thrombophilia should be counseled about the further increase in risk if they use HRT. It should be recommended that women who take HRT discontinue the therapy perioperatively or following trauma during the period of immobilization and restart HRT when they return to normal activity.[246] Women at very high risk of venous thromboembolism, such as those with cancer, disorders of blood viscosity, or a prior history of venous thromboembolism should avoid menopausal HRT.[244] An association has been shown between the use of HRT and MI in postmenopausal hypertensive women with the prothrombin 20210G→A variant. Confirmation of this finding in other studies may allow better risk assessment associated with HRT in women.[247]

12. Pulmonary Disease

At present, we have only little knowledge of the influences of sexual hormones on respiratory function. In fact, ERs (specifically ERβ) have only recently been found in lung, thus providing a rationale to further investigate new mechanisms for otherwise well-known pathologies.

12.1 Asthma in Postmenopausal Women

Estrogen may play a role in the pathophysiology of asthma. A prospective review of HRT and asthma incidence in premenopausal and postmenopausal women aged 34–68 years conducted during a 135 person-year followup of 1 year, 726 new cases of asthma were documented. Postmenopausal women with no previous history of hormone use had a significantly lower age-adjusted risk of asthma than premenopausal women (RR = 0.65; 95 percent CI 0.46–0.92.). Users of 10 or more years duration had twice the age-adjusted risk of asthma compared with women who never used HRT (95 percent CI = 1.39–2.87). There appears to be a positive dose response between the daily dose of CEE and asthma risk.[248] In a study in asthmatic women, it was demonstrated that peak expiratory flow was adversely affected by HRT.

In the treatment of asthma, inhaled corticosteroids have been shown to decrease serum osteocalcin levels in postmenopausal asthmatic women.[249] Although it is clear that oral corticosteroids can result in an enhancement of postmenopausal osteoporosis, inhaled corticosteroids (beclomethasone) have also been shown to disturb Type I collagen synthesis when high-dose corticosteroids are used.[250] It is unknown, however, whether inhaled beclomethasone impairs the ability of osteoblasts to form bone. It is also unknown whether there are any detrimental longer term effects on bone with prolonged inhaled corticosteroids.

12.2 Miscellaneous Conditions

Pulmonary lymphangioleiomyomatosis is a disease confined to women in their reproductive, years and there are some reports that hormonal factors play a role in the development of the disease before and after the menopause and that hormonal treatment may be beneficial in older women.[251] There is one report which suggests that estrogen medication without progesterone in postmenopausal heterozygous women with cystic fibrosis can cause false-negative tests. This report suggested a balance between progesterone and estrogen for cystic fibrosis lectin activity.[252] Obstructive sleep apnea syndrome has been associated with massive obesity in the appearance of this syndrome in women.[253]

13. Conclusions

CVD remains the commonest single cause of female mortality and morbidity in the Western World. Despite the apparent protection offered by endogenous sex hormones in their premenopausal years, the greater longevity of women exposes them to a similar lifetime risk of coronary and other vascular disease compared to men. Women tend to develop disease at a later age than men, and are more likely to have complicating co-morbidities such as hypertension and diabetes mellitus, which contribute to poorer short term outcomes following coronary events or revascularization. The atherogenic risk profile of older women is appreciably more adverse than that of younger women, though it is uncertain whether age or hormones are the primary determinant of the evolution of the adverse risk profile. HRT has been shown to consistently and markedly improve the lipid risk profile, though a benefit on cardiovascular outcomes, such as MI or cardiac mortality, has not yet been demonstrated. A lack of benefit may be due to countervailing adverse changes in coagulation or inflammatory mechanisms. In view of gender differences in atherosclerotic plaque and the vascular remodeling effects of estrogen and progesterone, HRT may still prove to have an important role in the management of CVD in women.

Except for asthma, there appears to be little impact of menopause or HRT on the pulmonary system although further research is warranted.

14. Future Needs

- RCTs are urgently required to investigate the potential benefits and risks of different hormone preparations (different estrogens, progestins, combinations, and routes of administration) in women with and without prior CHD. Low-dose oral estrogens, nonoral preparations, SERMs and androgens have to be investigated in trials with clinical outcomes.
- Future clinical trials of prevention treatments and treatments of existing disease should include sufficient women to allow for an adequate assessment of the effects in women and men.
- Except for asthma, very few data exist on the effect of the menopause or HRT on the respiratory system, and investigation of the effects on important disease entities should be considered.

CVD remains the commonest single cause of female mortality and morbidity in the Western World.

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Chapter 9: Osteoporosis and Oral Bone Loss in Aging Women: Risks and Therapy

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Osteoporosis affects a large proportion of the population of elderly women throughout the world.

Key Points[a]

1. Osteoporosis affects a large proportion of the population of elderly women throughout the world.
2. The loss of estrogen at menopause contributes significantly to skeletal bone loss, although the mechanism is not completely understood.
3. Although there has been major progress in methods for assessing risk for osteoporotic fractures, identifying individuals at greatest need of antiosteoporosis treatment remains an unmet need.
4. Low bone mass at menopause can be due to insufficient bone acquisition during growth or bone loss during adulthood. Adequate nutrition—in particular, but not exclusively, from intake of calcium and vitamin D—and adequate physical activity are the first line of prevention against osteoporosis [C].
5. ERT has been a mainstay in the prevention and treatment of osteoporosis for menopausal women in many countries. HRT has been shown to maintain bone density and favorably influence markers of bone resorption [A]; observational data and some, but not all, controlled clinical trials have demonstrated reduced fracture risk with estrogen or hormone treatment [B].
6. SERMs are two recently developed classes of drugs that have been shown to stabilize bone mass and prevent fracture in postmenopausal women [A]. The long-term effects of these agents are not known.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.)

7. A connection between menopausal estrogen deficiency and oral bone loss is biologically plausible, and many research findings to date [C/D] are consistent with that link. Some early findings support the hypothesis that treatments used to maintain or improve skeletal bone density may favorably affect oral bone status and attendant tooth loss.

1. Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.[1] It has been widely recognized in recent years by the medical profession and the public as a significant health concern, especially for elderly women, among whom osteoporosis is more prevalent than among men.[2] In most cases, bone loss proceeds for many years without any symptoms, and a fracture is often the first manifestation of the disease. Although rates of osteoporosis and associated bone fractures increase with age, research findings suggest that severe bone loss and fractures are not natural consequences of aging but may be prevented or substantially delayed.

Measurement of BMD is the most common clinical diagnostic method for assessing skeletal status and fracture risk.

Measurement of BMD is the most common clinical diagnostic method for assessing skeletal status and fracture risk. Dual energy x-ray absorptiometry (DEXA) of the hip and spine is the preferred measurement. It is validated by many studies, has the best precision, and is correlated with fracture risk. A WHO expert panel defined osteoporosis as a BMD at the hip more than 2.5 standard deviations (approximately 30 percent) below the peak mean BMD achieved by normal young adults.[3] This same panel defined low bone mass (osteopenia) as a BMD between 1 and 2.5 standard deviations below the young adult peak bone density. The intent of these definitions was to enable cross-cultural evaluation of bone mass, using culturally specific normal ranges. The definitions have allowed a more rational estimation of the numbers of people at risk for osteoporosis-related fractures in different countries and with different ethnicities. In some countries (especially the United States) these definitions have become accepted as diagnostic cut points. While this was not the original intent, it has been a useful development in an environment where reimbursement is still aligned to diagnosis.

Using the WHO definitions of osteoporosis and low bone mass, investigators have estimated that osteoporosis poses a threat for 28 million people in the United States, 80 percent of whom are women.[4] Nationally representative BMD measurements would allow estimations of the prevalence of osteoporosis and cost of osteoporotic fractures in any country. It is important to recognize, however, that BMD is only one of a number of factors that contribute to risk for fracture and that fracture risk is the most important information for deciding who needs treatment or intervention. Other factors that contribute to risk for fracture include age, sex, general nutritional status, genetic background, and overall physical condition. The combination of such factors and BMD measurement in risk assessment appear to be of powerful predictive value.[5,6]

2. Epidemiology and Economic Costs of Fracture

The clinical consequence of osteoporosis is bone fracture. While most common sites of fracture are the spine, hip, and wrist, most fractures increase in frequency with age, with the exception of skull fractures.[7] In addition to increased mortality, acute and chronic back pain, disability, loss of height, decreased quality of life, and significant financial and psychosocial costs are also associated with the fractures.[8] Estimates are from age 50 years onward there is almost a 40-percent lifetime risk for any fracture of the spine, hip, or distal forearm for white women and a 13-percent risk for white men in the United States.[9] At least 90-percent of all hip and spine fractures among elderly, white U.S. women can be attributed to osteoporosis as well as a significant proportion of all other fractures.[10] Less is known about fracture risk in minority populations, although African-American women and men have higher average bone mass values[11] and lower rates of fracture compared with white U.S. women and men.[11]

Rates of fracture and even the male:female ratio of fractures observed vary in different parts of the world.[12] In Europe, hip fracture shows an elevenfold range in apparent incidence among women and a sevenfold range among men between the various countries in data from 17 countries.[13] The highest incidence was found in the northern part of Europe, and the lowest was found in the Mediterranean area. The overall lifetime risk for any fracture in women older than 50 years in most European countries is approximately 30–40 percent,[14] similar to that for white women in the United States, despite the clear variability across cultures. In general, in Europe and elsewhere, the fracture rate is greater in urban areas than in rural areas.[15]

Vertebral fractures are notoriously difficult to detect and quantify. Lateral radiography of the spine may be required to determine their presence. Many fractures identified radiologically are asymptomatic or, even if painful, are not brought to medical attention. Only one-third of vertebral fractures present as clinically apparent fracture events.[14] Symptoms and signs (back pain, height loss, and kyphosis) are under recognized, in part because they are nonspecific. Radiological definitions based on changes in the height of vertebrae, used in clinical trials and in observational studies, can yield widely different estimates of prevalence.[16] In the United States, a prevalence of 25 percent in women over 50 years of age has been estimated.[17] The risk of vertebral fracture in U.S.[18] and Australian[19] women increases fifteenfold to thirtyfold between ages 50 and 90 years. (The risk increase for hip fracture across those years in women is fiftyfold.) Spine fractures also predict other fractures,[20] in particular subsequent spine fractures with the absolute risk of a second spine fracture being approximately 20 percent in the first year after the initial event.[21] In addition, spine fractures are associated with an increase in all-cause mortality rate.[22,23]

Medical expenditures for the treatment of osteoporosis-related fractures exceeded $13 billion in 1995, with the treatment of white women accounting for 75 percent of the costs.[24] As populations age and health care costs increase, the costs of osteoporosis-related fractures will only escalate. Projections based on population growth, particularly the marked increase in the elderly populations, suggest that fractures and their associated costs could triple in the United States by 2040,[25] and clearly this is a worldwide problem.[12] In many countries, especially in Scandinavia, there is an upward trend in fracture prevalence.[26] In part, the trend is due to the aging of the populations, with greater numbers of old and very old people in many populations across the world. However, clear age-specific increases, particularly in hip fracture rate, have been noted in the United States, the United Kingdom, and Scandinavian countries. In the United States, the increase appears to have plateaued.[27] Assuming no change in age- and sex-specific incidence, the annual worldwide total of 1.26 million hip fractures in 1990 is expected to double by 2025 as populations continue to grow older.[28] The greatest increases, due to demographic changes, are expected to be in Asia, in particular, in mainland China.[28]

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3. Pathogenesis of Fracture

Fracture is related to bone strength and to the force exerted upon that bone. Because bone mass and bone quality decline with age, less force is required to cause a fracture as age increases. Understanding the skeletal component of fractures requires an understanding of the process of bone remodeling. In addition, it is important to realize that a number of factors can contribute to fracture risk by increasing the likelihood of trauma and that they can be independent of bone mass.

3.1 Bone Growth and Remodeling

During childhood, bone grows linearly and can be reshaped to fit the stresses placed on it by the process of modeling. At the cessation of growth, modeling virtually ceases, and bone is continually replaced, but not reshaped, by remodeling, although modeling still occurs, for example, after a fracture, when realignment is necessary. Remodeling[29] can be thought of as a preventive maintenance program to ensure a strong, healthy skeleton, by old bone removal—performed by osteoclasts—and new bone deposition—performed by osteoblasts. Osteoclastic activity also fulfills the important role of calcium, mobilization from the skeleton, crucial which is to the maintenance of blood levels of calcium especially when the nutritional supply of calcium is insufficient. In such situations, bone mass will be lost in an attempt to provide adequate calcium in conditions of calcium deficiency.

The mechanism by which estrogen deficiency causes bone loss is still not completely understood.

Remodeling occurs in foci that are discrete in time and place.[29] It is a process initiated on the surface of bone; therefore, any disturbance of remodeling will preferentially affect sites with large surface areas. Consequently, with increased osteoclastic activity, bone is lost initially from the cancellous (spongy bone) component, which forms only 20 percent of the skeletal mass but provides 80 percent of skeletal surface area. Because there is considerable cancellous bone in the spine and in the ends of long bones, bone loss at those sites is greatest. Excessive bone removal at these sites can completely erode trabeculae, disrupting the architecture.[29] Once trabeculae (and their surface area) are lost, bone loss becomes more evident in cortical bone, especially consequently in later life.

During bone growth, bone mass is gradually accrued in a process that is heavily dependent on genetic factors.[30] It is likely that many genes control so-called peak bone mass, that is, bone mass in young adult life, including the genes that control body size. The search for a specific gene that controls peak bone mass, bone loss, or osteoporosis has been disappointing and will probably remain so. Peak bone mass is also powerfully influenced by factors affecting prenatal, and early childhood, and adolescent growth, including diet and lifestyle. Chronic illness, inadequate diet, or physical inactivity during childhood can reduce peak bone mass.

3.2 Impact of Menopause on Bone

After attainment of peak bone mass, bone density is fairly stable in most healthy premenopausal women. There may be some slow bone loss, particularly in the hip, but it is the gradual onset of ovarian failure that heralds the most dramatic changes in skeletal homeostasis. Bone loss accelerates markedly for a few years after natural menopause or oophorectomy, and some loss continues for the remainder of life.[31] Women with very low endogenous estrogen concentrations after menopause may be at particularly high risk for hip and spine fractures.[32] It has been proposed that estrogen deficiency is the cause of both the early, accelerated phase and, at least in part, the late, slow phase of menopausal bone loss.[33]

The mechanism by which estrogen deficiency causes bone loss is still not completely understood. After menopause, there is increased bone turnover, which by itself produces a transient, reversible loss of some bone tissue.[34] Irreversible bone loss is caused by an imbalance between the amount of bone removed by osteoclasts and the amount of new bone produced by osteoblasts within each remodeling cycle. Considerable attention has focused on the ways in which estrogen might modulate both turnover and remodeling imbalance. Several possible potential second messengers for estrogen's effects have been proposed. Osteoblasts or cells of the osteoblast lineage are thought to control the remodeling process. Communication between osteoclasts and osteoblasts may modify the amount of bone removed by the former cells, perhaps by controlling recruitment or the lifespan of the osteoclast population. Candidates as messengers include the interleukins (especially interleukins 1, 6, and 11), prostaglandins, insulin-like growth factors 1 and 2, TGF-β, and the rank/rank-ligand system.[34,35] Rank ligand is secreted by osteoblasts and mediates osteoclast recruitment and activity through rank, its receptor expressed in osteoclasts. Osteoblasts also secrete osteoprotegerin, a decoy receptor which mops up the ligand and has potential as a mechanism to inhibit osteoclast function and thus prevent bone loss.

It is known that bone loss continues into and may even accelerate in old age.[36] There has been much speculation on the role of estrogen deficiency in mediating the process. It seems evident that estrogen deficiency, plays a role but that, increasingly with age, other factors—including weight loss, physical immobility and frailty, calcium and vitamin D deficiency and secondary hyperparathyroidism, and the effects of intercurrent disease—come into play.

3.3 Falls and Bone Fragility

Multiple factors have been associated with an increased likelihood of falling and consequent fracture.[37] Age itself is a strong predictor for falls as individuals become increasingly frail. Other factors implicated with risk of hip fractures include cigarette smoking, low body weight (especially weight loss, perhaps a marker of frailty), previous fracture, and family history of hip fracture.[5] Of particular importance is a personal history of fracture as an adult. A history of peripheral fracture is usually easy to elicit, but determination of spine fracture may require lateral radiography of the spine. Spine fracture predicts risk for future hip fracture, independently of bone density.[20] A single spine fracture almost doubles the risk of hip fracture, and multiple spine fractures further increase the risk. Prevalent spine fracture increases risk for further spine fractures by a factor of 4 to 5. An incident spine fracture (i.e., a newly occurring spine fracture) further increases the risk, such that 20 percent of patients who present with a new spine fracture may be expected to have a second spine fracture within a year.[21]

4. Clinical Assessment and Diagnosis

For women after menopause, clinical evidence of osteoporosis should be sought at every clinical evaluation.

The initial approach to a patient with osteoporosis or one who may be at risk for osteoporosis is a complete history and physical examination. The physician should determine the presence of any underlying cause of osteoporosis, including the use of any medication that might affect the skeleton, such as thyroid hormone supplements or glucocorticoids. For women after menopause, clinical evidence of osteoporosis should be sought at every clinical evaluation. The principal method for making the diagnosis of osteoporosis is evaluation of the skeleton by a noninvasive measurement of bone density. In conjunction with the patient history and findings of the physical examination, bone density evaluation will determine whether the risk of fracture is sufficiently high to warrant pharmacological intervention. Bone density measurement can also serve to monitor bone loss or the effects of therapy, although its limited precision makes it somewhat less useful for individual monitoring than for risk prediction.[38]

Diagnosis of osteoporosis according to BMD criteria is dependent upon the site assessed (hip, spine, forearm, heel) and the methodology used.[39,40] Measurement in the hip by DEXA is preferred because it is less subject to the age-related artifacts that affect the spine and is a better predictor of hip fracture risk.[41] Where that modality is not available, x-ray absorptiometry or computed tomography may be used to assess the spine, forearm, tibia, or calcaneus. If these instruments are not available ultrasound, can also be used to assess fracture risk, but this modality has somewhat poorer precision and validation.[42]

At present, there are no internationally accepted guidelines for the use of bone densitometry to assess risk for osteoporosis. U.S. data, derived in part from cost-effectiveness analysis in white women, suggest that BMD should be measured in the following patient groups:[43]

1. All women 65 years of age or older, regardless of risk factors.
2. All postmenopausal women under 65 years of age who have, in addition to menopausal status, one or more other risk factors (thinness, current smoking, family history of osteoporosis-related fracture or a personal history of a fragility fracture).
3. Postmenopausal women who present with fractures (to confirm the diagnosis or determine the severity of disease).
4. Women who are considering therapy for osteoporosis, if the results of bone density evaluation would facilitate the decision.
5. Women who have received HRT for prolonged periods.

At present, there are no internationally accepted guidelines for the use of bone densitometry to assess risk for osteoporosis.

It would be cost-effective to be able to use a set of clinical risk factors to select women for bone densitometry. A Canadian group recently reported an assessment instrument based on only three factors—age, body weight, and current estrogen usage (yes or no). This instrument showed high sensitivity for selecting women with low BMD according to densitometry.[44] The approach of improved targeting may reduce the number of women who need densitometry for the identification of osteoporosis. In general, BMD measurement should not be performed if the findings would not influence a treatment decision. The presence of a disease (hyperthyroidism) or the use of a drug increasing the risk of osteoporosis (glucocorticoids, anticonvulsants) can also trigger referral for BMD measurement. More recently, an assessment tool for the risk of hip fracture was developed using the population from the study of osteoporotic fractures and was validated against a European cohort. This approach showed that clinical (and easily obtained) risk factors could identify individuals at increased risk of hip fracture and that the risk was amplified when BMD testing was added.[6,7]

5. Available Therapy

Efforts to reduce risk for osteoporosis should be encouraged among all adults. For those who are considered at high risk of fracture, pharmacological therapy may be required.

5.1 Nonpharmacologic Therapy

In general, risk factor reduction through nonpharmacologic means is considered sufficiently cost-effective that it should be instituted wherever possible in the general population.[43]

Avoidance of tobacco use and moderation in alcohol intake are obvious. All patients should also be encouraged to obtain an adequate calcium and vitamin D intake and to undertake a reasonable program of physical activity.

5.1.1 Calcium

Controlled clinical trials indicate that among the elderly, adequate calcium and vitamin D intake can reduce bone loss and potentially the risk of fractures, especially vertebral fracture.[45–47] In the only large trial with a hip fracture endpoint, dietary supplementation with calcium and vitamin D for 36 months significantly reduced hip fractures in elderly women whose average age was 82.[48] Calcium should be obtained as a nutrient from the diet to get the benefit of other components of food. Although calcium-fortified foods are becoming increasingly available, not all individuals will be able to increase calcium intake in this way. For those who cannot, supplementation should be encouraged. In the United States, the DRI—the recommended daily intake—for calcium is 1,200 mg for both women and men aged 51 years and older.[49] To achieve this goal, most menopausal women would need to add 500–750 mg of calcium to their usual intake. Selecting foods fortified with calcium can easily achieve this.

5.1.2 Vitamin D

There may be widespread deficiency of vitamin D in many populations, particularly the elderly, housebound, and institutionalized.[50,51] Inadequate exposure to sunlight, poor diet, and a decrease with age in the ability to absorb available vitamin D all contribute.[52] Because it is inexpensive to provide vitamin D and because many of the controlled trials of calcium also used vitamin D supplementation, supplements of vitamin D are recommended for at-risk populations. The recommended intake of vitamin D is 15 µg (600 IU/day) for persons > 70 years in the United States.[49]

On the other hand, there is a potential for vitamin D toxicity, and a dose of 2,000 IU or 50/lg per day should not be exceeded, except under close monitoring. The toxic effects of vitamin D overdose, mediated through hypercalcemia and hypercalciuria, include irreversible renal and cardiovascular damage due to the deposition of calcium in soft tissues.

5.1.3 Physical Activity

Most clinical trials have shown fairly modest and unsustained BMD responses to exercise in adults. The type of exercise that promotes a bone response may be different from the type recommended for aerobic fitness; it appears that muscle-building, weight-bearing resistance exercise is required to alter bone density.[53] For the frail elderly, exercise to reduce the risk for a fall is an appropriate intervention as muscle weakness is an important cause of falls. Muscle strength and neuromuscular performance can increase dramatically with proper exercise, [54,55] even in the tenth decade of life.[55] Consequently, where not medically contraindicated, increased physical activity should be encouraged. The most important feature of exercise is the requirement that it become a lifelong habit. Thus, it is better to recommend activities that the individual will enjoy than to provide rigid programs designed specifically to affect the skeleton.

New bone-specific drugs (e.g., bisphosphonates) and broad-spectrum drugs (e.g., SERMs) that combat osteoporosis and may have beneficial effects in other organ systems are available.

5.2 Pharmacologic Therapy

A decade ago, estrogen and injectable calcitonin were the only available pharmacologic therapies for postmenopausal women with osteoporosis. Now, new bone-specific drugs (e.g., bisphosphonates) and broad-spectrum drugs (e.g., SERMs) that combat osteoporosis and may have beneficial effects in other organ systems are available. PTH, the hormone that controls the mobilization of calcium, is emerging as a treatment with potential to add bone to an aging skeleton.

5.2.1 Estrogen Replacement Therapy

As discussed above (sec. 3.2), strong evidence supports the concept that postmenopausal estrogen deficiency precipitates bone loss. Controlled clinical trials have shown that ERT maintains bone density and has a favorable effect on markers of bone resorption.[56] Data from observational studies indicate that long-term use of estrogen reduces risk for nonspine fracture[57] and that discontinuation allows bone loss and waning of fracture protection.[57,58] However, there are only a few clinical trials of estrogen's effect on fracture, especially vertebral fracture.[59,60] One randomized, placebo-controlled trial in 464 early postmenopausal women without osteoporosis found a reduction in nonspine fractures over a mean period of 4.3 years in women assigned to estrogen or estrogen plus vitamin D.[61] However, in a trial of 2,763 women selected on the basis of presence of CHD, no difference was found in risks for nonspine fracture in women randomized to receive HRT compared with placebo.[62] A recent meta-analysis of the clinical trial data on the effect of HRT on the prevention of nonspine fractures showed an overall 27-percent decrease in nonspine fractures in women randomized to receive HRT, with the effect attenuated in women over 60 years of age.[63] Since this effect is so much less than expected from observational studies, it is possible that the reduced fracture rates with estrogen use reported in observational studies reflect the selective use of hormones by healthier women—women who, for example, smoke less, exercise more, and have a better diet. (See ch. 4 for bias.) Nevertheless, on the basis of long clinical experience, positive effect on BMD and bone turnover, limited fracture data, putative other benefits, and fairly low cost, estrogen has been considered one of the major medical options for menopausal osteoporosis prevention.

The first-generation bisphosphonate, etidronate, was shown in a small, placebo-controlled trial to reduce risk for spine but not nonspine fractures.

5.2.2 Selective Estrogen Receptor Modulator Therapy

SERMs are drugs that behave as estrogen agonists in some tissues, including bone, but behave as estrogen antagonists in other tissues, such as the breast. (See ch. 6.) SERMs include tamoxifen and raloxifene; the latter is the only SERM currently marketed worldwide for osteoporosis. In placebo-controlled trials, raloxifene prevented bone loss in healthy early postmenopausal women[64] and reduced risk for spine fracture in women with osteoporosis (RR reduction about 40 percent) but did not reduce risk for nonspine fractures in older women with osteoporosis.[65]

5.2.3 Bisphosphonates

The bisphosphonates are analogues of pyrophosphate in which the oxygen has been replaced by a carbon atom. They bind avidly to calcium hydroxyapatite in bone, with the potency of different bisphosphonates determined by the side chains on the carbon. The first-generation bisphosphonate, etidronate, was shown in a small, placebo-controlled trial to reduce risk for spine but not nonspine fractures.[66] Recent studies of newer more potent bisphosphonates have shown about a 45–50 percent reduced risk for spine fracture.[67–69] A reduction in the risk of nonspine fractures has also been demonstrated with both alendronate and risedronate.[67–70] Risedronate has been shown to reduce the risk of hip fractures in patients with osteoporosis in the only clinical study conducted thus far in which hip fracture was the primary outcome.[70] Alendronate and risedronate, but not etidronate, are marketed in the United States for the treatment and prevention of osteoporosis; etidronate is available in a number of other countries.

5.2.4 Salmon Calcitonin

The peptide hormone calcitonin is approved in the United States for the treatment of osteoporosis. Some clinical trials have shown a reduction in bone resorption and the preservation of bone mass.[71–74] In the major study completed thus far, calcitonin nasal spray, 200 IU per day, compared with placebo had modest but statistically significant effects on spinal bone mass and bone turnover and reduced, by 33 percent, risk for new spine fracture in postmenopausal women with osteoporosis.[74] This trial failed to show the effect of calcitonin on peripheral bone density or on the risk of nonspine fracture, furthermore, the 400 IU dose failed to show statistically significant reductions in spine fracture. Although there are no conclusive data on the effect of calcitonin on risk for nonspine fracture, an analysis of pooled results from several studies suggests that salmon calcitonin treatment might provide benefit.[75]

5.3 Considerations in Selecting Pharmacologic Therapy

Which pharmacologic agent to select in a given patient is a complex decision that must take into account whether the need is for the prevention or treatment of osteoporosis and for bone-specific or broad-spectrum effects, as well as patient acceptability and tolerability and the cost of the drug being prescribed.

5.3.1 Need for Prevention or Treatment

Theoretically, for maximum prevention of osteoporosis, drug therapy should probably be initiated at menopause and continued lifelong. However, there are as yet no data on the optimal duration of use for nonestrogen formulations, and long-term prevention is not easily achieved with estrogen therapy, requiring its continuation for 20 to 25 years after menopause.[57,76]

An observational cohort study of 9,704 U.S. women over 65 years of age showed a 71-percent lower RR for hip and wrist fracture and a 50-percent lower RR for all nonspine fractures among those who had started estrogen within 5 years of menopause and who were still taking it.[58] In this same study, the use of estrogen for more than 10 years had little impact on later fracture risk for elderly women who had stopped therapy. A cross-sectional study of 740 white U.S. women aged 60–98 years confirmed that 10 years of estrogen use, begun soon after menopause but stopped, had little effect on bone density many years later.[58] This confirms prospective data, which demonstrate that bone loss begins when estrogen is discontinued.[77,78] In an observational study of 47,050 U.S. women, Barrett-Connor and coworkers were able to separate duration of use from recency of use and found both factors to be important for optimal preservation of bone density.[79]

Until recently, it was a popular belief that 6 or more years after menopause was too late to achieve fracture benefit from any treatment. However, data from the late 1980s had shown that preservation of bone mass could be achieved among older women using estrogen.[80] Recent studies have confirmed those data and have shown substantial reductions in risk for fracture when HRT was initiated > 10 years after menopause.[57,58,60] Several large clinical trials have shown that antiresorptive therapy with bisphosphonates[67–70] or raloxifene[65] given to elderly women can rapidly produce substantial reductions in risk for spine fracture (60–68 percent reductions in risk within the first year, and 41–46 percent reductions over 3–4 years). With such excellent responses to treatment when started many years after menopause, it is not surprising, therefore, that the National Osteoporosis Foundation's cost-effectiveness analysis suggests that the ideal time, from the viewpoint of use of medical resources, for women to begin an osteoporosis drug is at age 60 to 65 years.[43] Early postmenopausal prevention using bone-specific drugs is not considered cost-effective because, on average, the incidence of fracture among women remains low until the age of 65 years or more. (See "Cost-Effectiveness" below.) Drug treatment with bone-specific agents may be most effective in those who have osteoporosis, by BMD criteria.[76] Therapy begun after age 80 years in frail individuals may not be effective in reducing hip fracture risk, and in the very elderly, interventions aimed at reducing the impact of trauma, such as hip protectors, would be preferred.[81]

The ideal time, from the viewpoint of use of medical resources, for women to begin an osteoporosis drug is at age 60 to 65 years.

How should this information be incorporated into clinical practice? By targeting for treatment women in whom clinical evidence of osteoporosis has already appeared (height loss, fracture) or who have very low BMD (more than 2.5 standard deviations below the mean value for young adults), treating physicians can make the most efficient use of limited medical resources. Because it appears that bisphosphonates work well to reduce fracture risk in patients with osteoporosis,[68–70] bone density can be used as an indicator for treatment. It may also serve as a patient-motivator; acceptance of HRT was higher in women who had undergone BMD measure, regardless of the result, than in those who had not,[82] and awareness of low bone density has been shown to enhance acceptance of osteoporosis treatments.[83,84]

The reasons for women wanting or refusing to take estrogen are complex. HRT is usually begun close to menopause for symptom relief, and women will often continue it for these tonic effects.

5.3.2 Need for Bone-Specific or Broad-Spectrum Effects

Broad-spectrum therapies, such as estrogen and raloxifene, are thought to act as "health packages" that include improvement of the plasma lipid profile and, possibly, protection against other common diseases of aging. In many instances, however, trial data are not yet available to support the claims for clinical endpoints. Although bone-specific drugs, such as bisphosphonates, appear to provide greater fracture risk reduction than broad-spectrum drugs, especially for nonspine fractures, many postmenopausal women want or need interventions for other health concerns.

5.4 Acceptability and Tolerability

The reasons for women wanting or refusing to take estrogen are complex. HRT is usually begun close to menopause for symptom relief, and women will often continue it for these tonic effects.[85] Older women, on the other hand, typically begin hormones and other treatments for health promotion, particularly for prevention of osteoporosis-related fractures.[85]

Long-term drug therapy requires a high degree of patient acceptance—one that is predicated on the patient's perception that treatment benefits outweigh risks and that treatment is convenient, low in cost, and free of side effects. Among U.S. women > 60 years of age, it was found that 68 percent and 48 percent who started estrogen or raloxifene, respectively, had stopped within 24 months.[86] A similarly high discontinuation rate was found in U.S. women who had started alendronate.[87] Side effects are the main reason for stopping antiosteoporosis drugs. Vaginal bleeding and breast tenderness rank high among reasons that older women give for stopping HRT.[85] Gastrointestinal symptoms are the most common reason for stopping alendronate, while vasomotor symptoms are the reason cited by women for discontinuing raloxifene.[65] There are as yet no data on continuation of risedronate. Poor continuation is not fully explained by side effects: nearly one-third of relatively asymptomatic women who complied with a HRT trial regimen for 3 years discontinued the therapy within 2 years after the trial's end.[88] In general, discontinuation rates in clinical settings are several fold greater than those reported from clinical trials; it is likely that patient selection plus the education, motivation, and support provided to participants by clinical trial staff account for some of the differences.

Gastrointestinal side effects with alendronate are more common in women over 70 years of age and in those with active upper gastrointestinal problems, such as gastroesophageal reflux disease or with current nonsteroidal anti-inflammatory drugs (NSAIDs) use.[89] These risks of developing gastrointestinal symptoms may be reduced if patients adhere to dosing guidelines. In other patients who exhibit upper gastrointestinal symptoms while taking alendronate, administration of the medication weekly may improve tolerability. Once-weekly alendronate 70 mg yielded the same effects on BMD and bone turnover as daily alendronate 10 mg.[90] Risedronate may be less apt to cause gastrointestinal lesions.[91]

5.5 Cost Effectiveness

It is clear that greater treatment focus should be on women aged 60 years and older, who are on average 10–15 years postmenopausal. On the basis of age alone, they have a substantially higher risk for fracture than younger women. They also are more likely to have accumulated risk factors, including spine or other osteoporotic fractures. Moreover, older women may be more willing to begin and continue osteoporosis treatment because they correctly perceive that their risk for fracture is more immediate than the risk in younger women. Osteoporosis drugs should be reserved for patients at high proximate risk for fracture. By targeting women over 65 years of age and who have multiple risk factors or all women who have clinical evidence of osteoporosis (height loss, fracture), treating physicians can make more efficient use of limited medical resources and can expose fewer women to drugs whose long-term effects remain uncertain.

5.6 Clinical Perspective on Drug Selection Issues

If pharmacologic therapy is indicated for prevention of osteoporosis, estrogen is probably the best choice for early postmenopausal women, because it is low in cost, provides relief of climacteric symptoms, and perhaps lowers risks for certain other diseases of aging. For women at high risk of fracture and in need of treatment—typically those who are elderly with fractures—a bisphosphonate might be considered more appropriate. For many women between these two extremes, who have a moderate risk of fracture (especially vertebral fractures) and who are also seeking other health benefits (reduced risk of breast cancer), raloxifene might be preferred.

Now that a number of effective osteoporosis therapies have become available, two new questions have arisen regarding their use: Should they be combined? How long should they be continued? The therapies in use today are all antiresorptive, and their effects on bone turnover are additive to a degree. For example, estrogen alone or alendronate alone will suppress bone turnover 50–55 percent on average; when added together, bone turnover is suppressed 65–70 percent.[92] The increment in bone density achieved with combination therapy is small, about 1–2 percent over the usual 5-percent increment with either treatment used alone. There are no data to show greater efficacy in fracture reduction, and there is concern that oversuppression of bone turnover could contribute to greater fracture risk by either causing hypermineralized, brittle bone or by impairing bone repair and renewal.[93] The added cost, complexity, and potential side effects also are reasons to exercise caution in the use of combination antiresorptive therapies. However, future study of low dosages of two antiresorptive therapies is warranted; this could produce the desired bone and other effects with lower cost and better tolerability and potentially reduce the adverse effects of these drugs.

In the future, we are likely to see the use of osteoporosis drugs in sequence; for example, a bone anabolic drug (see below) might be used for 1–2 years to stimulate new bone formation, and an antiresorptive drug would be used subsequently to consolidate and maintain the bone gains.

Osteoporosis drugs should be reserved for patients at high proximate risk for fracture.

Choosing the right drug regimen for the right woman involves assessment of short-term fracture risk and other nonskeletal health issues. By understanding available regimens and customizing the therapy to the needs of each woman, clinicians are more likely to achieve clinical goals and optimize the chances for long-term continuation. With the emergence of proved treatment alternatives, it is no longer acceptable to use a "one size fits all" approach to the years after menopause.

6. Novel Therapeutic Options

Options in development for the treatment of osteoporosis range from Kyphoplasty™ (a method for filling collapsed spine bodies with a cement) to hip pads designed to reduce the energy transmitted to the hip during a fall. Some potential pharmacologic agents are variants of available agents; others seek to interfere with novel targets in the osteoclast population or to stimulate new bone formation.[94]

Options in development for the treatment of osteoporosis range from Kyphoplasty™ … to hip pads designed to reduce the energy transmitted to the hip during a fall.

One very promising approach is the use of PTH. Among menopausal women with osteoporosis who were already receiving HRT, the addition of daily subcutaneous PTH markedly increased spine BMD during years of treatment, compared with no significant change in the group receiving HRT alone.[95] Total-body bone mineral was also increased, with no detrimental effect at any skeletal site, and the increased bone mass was associated with a reduction in rate of spine fracture. The findings were confirmed in a larger study of 1,673 women with osteoporosis and existing spine fractures.[96] Compared to those receiving placebo, those receiving 20 µg recombinant 1—34 PTH subcutaneously and daily, for an average of 18 months, had marked reductions in spine and nonspine fracture risk; a 65-percent reduction was observed for spine fracture, and a 52-percent reduction was observed for nonspine fractures. This very promising therapy, in addition to increasing bone density, increases the area of vertebra and the diameter of peripheral bones. The early and profound fracture reduction may be due, in part, to changes in bone geometry and integrity.

The development of many more therapeutic alternatives can be anticipated as understanding of the genetics and pathophysiology of osteoporosis continues to grow.

7. Oral Bone Loss

Oral bone, like the rest of the skeleton, comprises both trabecular and cortical bone and undergoes formation and resorption throughout the lifespan. Unlike the case of the postcranial skeleton, however, fracture rarely results when oral bone loss exceeds gain. Generally, oral bone loss manifests as either loss of tooth-anchoring support or as a diminution of the remaining ridge in areas of partial or complete tooth loss. Residual ridge resorption refers to the loss of oral bone subsequent to the natural loss or removal of teeth. Its rate and extent are highly variable. Progressive residual ridge resorption can interfere with the placement of implants and can result in an inability to stabilize dentures.[97]

Given the chronic and progressive nature of oral bone and attendant tooth loss and the fact that symptoms often do not appear until advanced stages of disease, painful and handicapping outcomes are highest among people in later stages of life. Many older adults report changing the composition of meals, taking a long time to complete a meal, being deterred from eating with others, and feeling social discomfort in smiling, singing, or kissing as a consequence of poor oral health.[98] In fact, the literature is replete with examples of not only the physical but economic, social, and psychological consequences of oral diseases.

7.1 Epidemiology

Analyses of U.S. data from the NHANES III indicate that, among women > 18 years of age, 63.8 percent have experienced loss of one or more teeth excluding third molars and 67.1 percent have evidence of moderate periodontal disease, defined as loss of bony tooth support of 2 mm or more.[99] Furthermore, the prevalence of these conditions increases with age in both sexes. Data from the WHO's Global Burden of Disease Study (GBDS) provide a unique opportunity to examine the prevalence of edentulism across eight global regional groupings. Differences in disease definitions and methods prohibit direct comparisons between NHANES and GBDS data, but the global study provides evidence that the condition accounts for significant morbidity worldwide. For example, within the grouping identified as Established Market Economies which includes North America, Western Europe, and Australia, it is estimated that 95 million people were edentulous in 1990.[100] Epidemiologic data for residual ridge resorption are lacking, but clinical impressions suggest that more women than men present with severe residual ridge resorption requiring specialized treatment.

7.2 Etiology

The multifactorial nature of oral bone and tooth loss make it difficult to unravel the roles of gender biology, longevity, and health care utilization in their pathogenesis. Women are reported to be more inclined to self-care, more likely to visit a dentist, and more likely to report symptoms such as pain.[101,102] The degree to which such behaviors influence oral disease patterns and health statistics is unknown. For instance, to what extent is tooth loss the result of primary disease experience or dental treatment? And do anecdotal reports of women's greater experiences with severe residual ridge resorption reflect real differences in morbidity or sex differences in longevity and illness behavior?

Despite these voids in understanding, there is a growing body of literature that indicates that oral bone and attending tooth loss are associated with menopausal estrogen deficiency and osteoporosis.[103–123] Not all studies in the topic area have yielded positive results, however.[124–128] Differences in study design—including in population, sample size, approach to skeletal and oral bone assessments, definitions of outcomes, and adjustment for confounding variables—are likely reasons for conflicting findings.

Still, data emerging from controlled clinical studies provide evidence of a significant association between oral bone status and skeletal status.[129–131] These include preliminary findings of a 7-year longitudinal study of osteoporosis and oral bone loss being conducted at the University of Alabama at Birmingham in a subsample of participants ($n = 457$) enrolled in the observational component of the WHI of the NIH.[129,130] As part of the study protocol, comprehensive medical history and examination data from the core WHI, including hip BMD as determined by DEXA, are linked with oral examination findings and oral bone density measurements by the validated technique of digital subtraction radiography. Analyses of cross-sectional baseline data indicate a strong and significant correlation between hip BMD and lower jaw bone density ($r = 0.78$, $p < 0.001$).[129] Furthermore, preliminary analyses of longitudinal data from the first 85 participants to return for their 3-year followup appointment indicate that the association is clinically important.[124]

It is estimated that 95 million people were edentulous in 1990.

Among participants with evidence of periodontal bone loss at baseline, those with hip BMD > 1 standard deviation below the reference value for healthy young women had a significantly higher rate of progressive oral bone destruction than participants with hip BMDs within 1 standard deviation of normal ($p < 0.05$).

Data on the relation between skeletal BMD and tooth loss are not yet available from the described WHI cohort, but other studies have examined this issue. The Study for Osteoporotic Fractures Research Group reported an association between tooth loss and the rate of systemic bone loss among 4,524 U.S. women age > 65 who reported being dentate at baseline and who returned approximately 5.7 years later for a followup visit. On adjustment for age, weight, use of estrogen, and smoking status, it was found that women reporting tooth loss had higher annual decreases in hip BMD than women who did not lose teeth (0.68 percent versus 0.54 percent, $p < 0.0029$).[132]

7.3 Approaches to Therapy

Bone regenerative procedures, such as guided tissue regeneration and grafting, have already become commonplace for treatment of localized oral bony defects, and their use is likely to expand. State-of-the-art treatment for tooth loss focuses on the placement of single or multiple teeth implants; this approach, too, is gaining wide acceptance. Long-term studies are underway to evaluate the effect of antibiotics on progressive oral bone loss. Another promising area of research is the use of NSAIDs[133] and bisphosphonates[134] to control host inflammatory and/or bone resorptive responses.

There are several important clinical implications of an association between oral status and skeletal status.

Given the data relating oral bone loss and osteoporosis, it has been hypothesized that treatments used to maintain or improve skeletal bone density may favorably affect oral bone status and tooth loss. Two large cohort studies have examined the effect of HRT on reported tooth loss.[135,136] Analysis of data on 48,483 participants in the Nurses' Health Study in the United States[136] showed that among women who reported regular dental visits there was an inverse relation between current hormone use and loss of teeth after controlling for age and cigarette smoking. Among the 3,921 women in the Leisure World Cohort Study who provided suitable data with which to assess tooth status, estrogen users had significantly lower age-adjusted tooth loss and edentulism rates compared with nonusers.[111] Studies of the effect of other bone-enhancing agents on tooth loss have been limited, but some trials have demonstrated positive findings. Data obtained from women with normal spine densities enrolled in a randomized nutritional intervention trial indicate that a smaller proportion of women taking calcium supplements reported tooth loss compared with those taking placebo.[137] A pilot trial has provided evidence of a lower RR for progressive oral bone loss among alendronate-treated participants than in placebo controls.[138]

7.4 Clinical Perspective on Oral Bone Loss

There are several important clinical implications of an association between oral status and skeletal status. On one side of the issue, it is possible that oral examination and radiographic findings may be useful signs of extra-oral bone diminution. Although preliminary studies along these lines have yielded promising findings, it is too early to know the value of routine dental visit information in signaling the need for skeletal bone evaluations.[139] On the other side, history of skeletal osteopenia may impact the need for, and outcome of, a variety of periodontal and prosthetic procedures including guided tissue regeneration and tooth implantations. If therapy for skeletal bone conditions is undertaken and is successful, the oral cavity may reap benefits as well.

A connection between menopausal estrogen deficiency and oral bone loss is biologically plausible, and many research findings to date are consistent with that link. More research is needed to contextualize the relation fully and to understand the extent to which menopause increases a woman's oral health risks. Even as we await more detailed information, women and their health care providers are advised to incorporate oral health into the menopausal conceptual milieu.

8. Future Needs

- We must improve methods for identifying people at risk for fracture; develop inexpensive and accurate machines to measure BMD and bone structural integrity; develop simple clinical means for determining risk of serious falls; and validate algorithms that combine clinical risk factors, bone density, and so forth, to accurately predict an individual's fracture risk in the next 5–10 years.
- Improve interventions; finding ways to enhance long-term compliance with calcium, vitamin D, and exercise; develop drugs that stimulate bone formation, which will restore bone mass and bone structural integrity; learn how to use drugs in combination or in sequence; have a better understanding of the optimal time to start drugs, how long to use them, and effects of their withdrawal; and know more about the long-term safety of drugs, that cumulate in bone, for example, bisphosphonates.
- Understand skeletal factors responsible for maintaining bone mass and bone strength, in particularly bone cytokines and growth factors, the effects of mineralization and hypermineralization on bone strength, and the way that bone anabolic agents signal bone cells.
- Improve tests that monitor bone health, including densitometric, ultrasonographic, and biochemical tests.
- Understand the relationship between oral bone loss and loss in the rest of the skeleton.
- Find therapies that will reduce bone loss that occurs early in life before osteoporosis becomes a clinical problem.

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